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Atopic dermatitis severity : risk factors and impact on quality of life

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Atopic Dermatitis Severity – Risk Factors and Impact on Quality of Life

A thesis submitted to the University of London

in partial fulfilment for the degree of

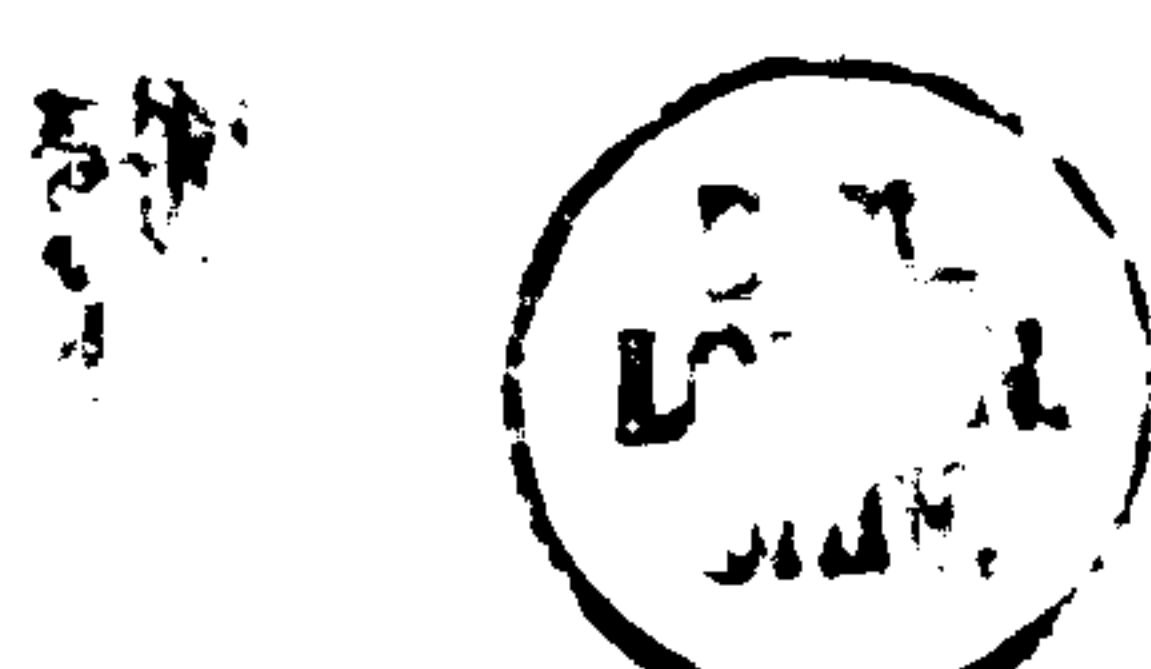
Doctor of Philosophy

By

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October 2001



Abstract

Atopic Dermatitis Severity - Risk Factors and Impact on Quality of Life

Atopic dermatitis (AD) is a chronic relapsing inflammation of the skin, which occurs in genetically predisposed individuals, with unknown aetiology and no cure. The prevalence has increased over the last three decades and shown to be higher in an urban area. But there is little known about factors that may affect disease severity. Comparing rural and urban populations may help in identifying those factors that may have an effect on disease severity. There is also scarce information about the impact of AD on children and family's quality of life (QOL), especially from a community-based study. The absence of any standard severity and QOL assessment system has hampered performing such studies. It is only in the last 10 years that dermatologists have tried to measure eczema severity and its impact in a systematic way. The association between increased disease severity and impaired QOL strengthens claims for more research into this disease.

A longitudinal study design was implemented in evaluation of risk factors for atopic dermatitis severity and its impact on QOL, which was a comparison of two populations recruited through general practices in South London and mid Wales. In children aged 5 to 10 years. GPs were asked to create a list of patients under a code of eczema or dermatitis from their database. Repeat prescriptions for emollients and/or topical steroids were also used by some of the GPs to create a list of potential patients. Parents were contacted by post and the diagnosis in their children was verified by the UK diagnostic criteria for AD. Parents filled in a locally constructed and piloted questionnaire to gather information about potential risk factors and confounders. AD severity was assessed using the SCORAD Index. The Dermatitis Family Impact (DFI) and Children Dermatology Life Quality Index (CDLQI) were used to measure family's QOL and children's QOL respectively on two occasions six months apart.

The aim was to determine those factors that might have an effect on the severity of AD, to document the impact of eczema on the family and children's QOL, and to investigate the relationships between QOL and disease severity. The ultimate goal was to improve the management and help in prevention of AD.

One hundred and thirty-seven children (52.6% females) with atopic dermatitis were recruited from a community setting, 82 (60%) urban and 55 (40%) rural. These children were examined up to four times and 120 (88%) attended the final visit. The study has demonstrated that eczema was mild in most cases (80%) and requires GPs care only. From this sample it has been shown that the following factors have been associated with increased risk of severe disease: living in an urban area, early onset of eczema, and child's asthma and or hay fever (atopy). It also showed that black children were at higher risk of severe AD than their white counterparts, a risk that can be masked by reliance on erythema scores. These findings may improve our understanding and may help in prevention of this disease.

Childhood atopic dermatitis had affected the children's QOL in more than two-thirds of children and has affected the families' QOL in more than one-thirds of the children. QOL scores both by children and families were significantly correlated with disease severity at single points of time and longitudinally. This shows the importance of considering patients' and their families' perceptions of the disease in understanding impact. It also reflects the construct validity of the CDLQI and DFI and that therefore, they can be used in studies to quantify the impact of AD on QOL of children and families respectively.

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1. Professor Rod J Hay
2. Doctor Catherine H Smith

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Dedicated to

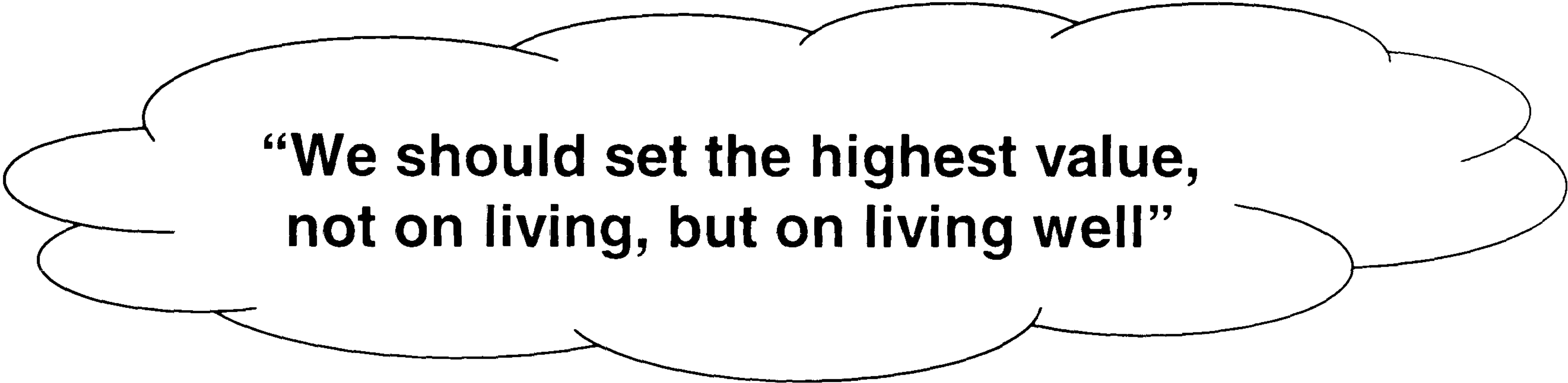
My father

*(Abullassad Abdullah Ben Gashir who died suddenly on the 9th of September 2000)
For his help and encouragement “throughout his life” for my study,
which made this thesis an achievable task. Without his help, it would
have been difficult, if not impossible, to continue my postgraduate study.
“God Bless You Father”*

&

My mother

For her continuous care, perceptiveness, and assurance.



**“We should set the highest value,
not on living, but on living well”**



Socrates

List of abbreviations

AD	A topic D ermatitis
CDLQI	C hildren's D ermatology L ife Q uality I ndex
CI	C onfidence I nterval
DFI	D ermatitis F amily I mpact
DLQI	D ermatology L ife Q uality I ndex
GP	G eneral P ractitioner
IL	I nter L eukine
P	P -value
OR	O dds R atio
QOL	Q uality O f L ife
R	R egression coefficient
r	C orrelation coefficient
r²	The square of the correlation coefficient – sometimes called the coefficient of determination
SCORAD	SCOR ing A topic D ermatitis
SCORAD-D	O bjective SCORAD (O bserver scores only)
SD	S tandard D eviation

1 CHAPTER 1 INTRODUCTION

1.1 Section 1: History, nomenclature, definitions, and prevalence

1.1.1 History

Atopic dermatitis (AD) is a chronic relapsing intensely pruritic disease, which occurs in genetically predisposed individuals. It usually starts at an early stage of life, but at times its onset may be delayed until adolescence. It is common in individuals with bronchial asthma, hay fever, or urticaria (Rajka., 1989a). Pharaoh Menes of Memphis, who may have had anaphylaxis following an insect sting in 2900 BC, was probably the earliest allergic subject and may be the first documented case of atopic dermatitis (Avenberg and Harper., 1980). The Roman historian Suetonius (born about A.D 69) precisely described the signs and symptoms of atopy in Emperor Augustus Caesar (63BC to 14A.D) who was suffering from intensely itchy lichenified skin, bronchial asthma and rhinitis (Mali., 1975).

1.1.2 Nomenclature

The name “atopic dermatitis” was first proposed by Wise and Sulzberger (1933) but before this, the medical literature had many synonyms for the disease. In 1884, Ferdinand von Hebra uses the term “prurigo” to describe an itchy papular eruption that began in early childhood, localised in flexures, and persisted throughout life (Hebra., 1884, cited in: Sehgal and Jain., 1993). Jean Louis Brocq (1856-1928) and Lucien Jacquet (1860-1914) named the disease “neurodermatitis” because of nervous system involvement in its dominating pruritic symptoms (Brocq and Jacquet 1891). In 1892 Ernest Besnier used the term “prurigo diathesique” to describe an itchy papulovesicular eruption which changed in morphology after a few years to

thickened and lichenified lesions that was associated with bronchial asthma and hay fever, and was accepted as a distinct entity after this report (Besnier., 1892). Thereafter “Besnier’s prurigo” was proposed as an acceptable name by Rasch in 1913 who confirmed Besnier’s description of prurigo diathesique (Rasch., 1925). In the early 1930s this disease entity was named atopic dermatitis (Wise and Sulzberger., 1933). After that, Hill and Sulzberger classified atopic dermatitis into infantile, childhood, and adolescent/adult phases. They suggested that in order to maintain this dermatological manifestation as an entity, from other nonatopic eczemas, it is best named atopic dermatitis of the infant, of the child, and of the adult (Hill and Sulzberger., 1935).

However, the nomenclature of atopic dermatitis varies from one speciality to another and from one country to another with the most used synonyms for atopic dermatitis being atopic eczema and infantile eczema. Despite the advance in naming the disease, the nomenclature of atopic dermatitis does not specifically reflect the dry, scaly and itchy features of the disease (Sehgal and Jain., 1993). Atopic dermatitis or atopic eczema is a name that is accepted world wide to describe the disease entity. Until a better understanding of the disease is achieved, atopic dermatitis or atopic eczema serves the purpose of indication of this entity and makes communication universal (Williams., 2000a).

1.1.3 Atopy

Atopy is a Greek word meaning without place or strange and was suggested by Professor Edward D Perry of Columbia University and applied by Coca and Cooke to describe this syndrome (Coca and Cooke., 1923). The first description of atopic hypersensitiveness was in 1923 by Coca and Cooke as

an individual propensity to develop what were subsequently found to be IgE-dependent reactions against environmental allergens (Coca and Cooke., 1923).

It is nearly 8 decades since the first description of atopy by Coca and Cooke. Atopy may be redefined taking into consideration modern immunological knowledge. The recent definition should include the respiratory syndrome of asthma and rhinitis, atopic skin manifestations which share genetic predisposition, hyperreactivity of the target organ to pharmacological agents (cholinergic hyperreactivity and beta-adrenergic hyperresponsiveness) or irritants, and an immunological Th2-Cell response to allergens (exogeneous or endogeneous) with facultative specific IgE production, and eosinophil activation (Wutchirch., 1999).

1.1.4 Atopic dermatitis definitions

1.1.4.1 Hanifin and Rajka criteria for atopic dermatitis

The last two decades have witnessed the development of a standard definition for this mysterious disease. Hanifin and Lobitz (1977b) proposed a list of clinical features to form the diagnostic criteria for atopic dermatitis. In 1980, Hanifin and Rajka have made revisions of the previous criteria that were based on practical experience, proposal and discussion by various individuals. They described the Hanifin and Rajka criteria for atopic dermatitis, which are based on a list of clinical signs and symptoms of AD. These comprise 4 major and 23 minor criteria named after them (see Appendix 6.5). A subject should have 3 major plus 3 or more minor criteria for the satisfactory diagnosis of atopic dermatitis (Hanifin and Rajka., 1980). The Hanifin and Rajka criteria have represented the corner stone for the

definition of individual cases of AD. Even though the criteria of Hanifin and Rajka are widely used in the diagnosis of atopic dermatitis, they may be less suitable for use in population-based studies in which their validity and agreement between and within observers are unknown (Williams., 2000a). Also, the long list of minor criteria would make it very difficult to use in epidemiological studies where the study requires collecting data from large numbers of subjects in a limited time.

1.1.4.2 The UK Working Party’s Diagnostic Criteria for Atopic Dermatitis

The need for a valid definition for AD motivated a group of dermatologists from the UK to develop a set of criteria with known validity that could be used in epidemiological studies. After serial testing of the Hanifin and Rajka criteria (1980), the group proposed the UK working party’s diagnostic criteria for atopic dermatitis (Williams, Burney, Hay, *et al.*, 1994a; Williams, Burney, Strachan, *et al.*, 1994b; Williams, Burney, Pembroke, *et al.*, 1994c), see Table 1. Five out of the 6 UK diagnostic criteria for AD are questions and in order to qualify, as a case of AD the subject must have one major and three minor or more criteria.

Table 1. The UK diagnostic criteria for AD

Must have one major “An itchy skin condition in the last 12 months”	
Plus three or more of the following minors	
1	History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles, or neck.
2	A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative, in those under 4 years).
3	A history of a generally dry skin in the last year.
4	Onset under the age of 2 (not used if child is under 4)
5	Visible flexural dermatitis (or dermatitis involving the cheeks or forehead and outer limbs in children under 4)

When tested on patients from the hospital the UK diagnostic criteria had 87.9% sensitivity and 92.8% specificity. In a community study, the sensitivity decreased to 80%, but the specificity increased to 97%, when compared with dermatologist diagnosis. Positive and negative predictive values were 80% and 97% respectively (Williams, Burney, Pembroke, *et al.*, 1996).

1.1.4.3 Other criteria

In recent years other dermatologists have proposed different criteria to define AD. Schultz-Larsen *et al* in 1996 have developed and validated a self-administered questionnaire that ascertain AD in children by asking parents about the presence of physical and historical features (Schultz-Larsen, Diepgen, Svensson., 1996). Recently another set of criteria was developed based on atopic features of AD (IgE response to allergens) called the “millennium criteria” for diagnosis of AD, which has two components. The first component (the mandatory criterion) is the presence of allergen-specific IgE. The second component comprises a set of principle criteria, (2 of 3 must be present): pruritus, chronic or chronically relapsing course, and typical distribution and morphology of eczema lesions “infant, childhood, or adult type”. However, if the distribution is not typical, it is important to exclude other entities (e.g. contact dermatitis, or contact urticaria). These authors proposed an additional criteria that should be used in case of doubt (Bos, Van Leent, Sillevis Smitt., 1998). The fact that 20-40% of individuals with typical clinical AD exhibit normal values of total or specific IgE (Dotterud, Kvammen, Lund, Falk., 1995), would probably make this definition redundant in a significant proportion of AD patients. Even so, it might be helpful if a better understanding of AD immunopathology were available.

1.1.5 Prevalence

The prevalence of atopic disorders (atopic dermatitis, allergic rhinitis, allergic asthma) has shown a marked increase over the last four decades, and this finding so far has remained unexplained. Environmental factors and individual parameters such as life style factors are thought to have contributed most to this trend (Williams., 1992). Taylor *et al* reported an increase in the prevalence of atopic dermatitis from 5.1% in children borne in 1946 to 7.3% in those born in 1958 to 12.2% in the 1970 cohort. This was based on parental recall when children were aged 5-7 years (Taylor, Wadsworth, Wadsworth, Peckham., 1984). Schultz-Larsen (1993) using a twin population in Denmark, also found that the cumulative incidence rate of twin individuals who develop atopic dermatitis between 0 and 7 years of age rose significantly from 3% in twins born between 1960-64 to 12% in twins born in 1975-79. Each case was identified by recall of eczema as a child according to the patients and/or parents, and the diagnosis was verified by a questionnaire (Schultz-Larsen, Holm, Henningsen., 1986; Shultz-Larsen., 1993).

In a follow-up analysis of the 1970 British National Cohort Study, 12.3% of five-year-olds were reported as having had eczema at some stage during their lives, and in 5% the condition was reported to have been present in the 12 months prior to interview (Golding and Peters., 1987). In studying AD and birth factors, Olesen and colleagues documented a 18.7% cumulative incidence of AD at the age of 7 years (Olesen, Ellingsen, Olesen, *et al.*, 1997).

From a community-based study it has been reported that the 1-year prevalence of AD was 16.5% (95%CI: 14.7 to 18.2%) with 84% in a mild form, 14% moderate and 2% in a severe form. The authors also showed that only 6% of the cases were referred to secondary health care services. Of those referred, 82% were in a mild and moderate form (Emerson, Williams, Allen., 1998). These figures show that the vast majority were under GP's care.

Based on clinical examination by an experienced dermatologist, Schafer *et al* (2000) showed that the overall prevalence of atopic dermatitis in East and West Germany was 10.4% in the 5 to 6 years old pre-school children. The prevalence was 12.9 in East Germany that was significantly higher than the 8.2% in West Germany (Schafer, Kramer, Vieluf, *et al.*, 2000). The authors showed that the prevalence has decreased in East Germany from 17.5% in 1991 to 11.2% in 1997 by repeated cross-sectional studies in 1991, 1994 and 1997. It is not clear whether the investigators had followed the same group or if they recruited new patients each time. The authors also reported (Schafer *et al.*, 2000) that children whose parents had a higher level of school education were affected more frequently, which is in agreement with Williams' finding in the UK (Williams, Strachan, Hay., 1994d).

A recent study on schoolchildren from urban and rural areas in Oregon, America (Laughter, Istvan, Tofte, Hanifin., 2000) showed that the overall prevalence of atopic dermatitis was 17.2% using the standard scoring criteria for the Schultz-Larsen Questionnaire (Schultz-Larsen, *et al.*, 1996) and 6.8% according to highly stringent criteria using dermatological examination (Laughter, Istvan, Tofte, Hanifin., 2000). However, the latter study had a low response rate (32%) especially from the urban area.

In general, the prevalence of AD is reported to range from 2 to 20% or even higher and peaks among infants and children than in adults (Hanifin., 1992), and even in adults AD is clearly predominant in younger persons (Schmied and Saurat., 1991). However, there is still insufficient prevalence data from the UK based on examination by dermatologists of prospectively defined populations (Williams., 2000a).

1.1.6 Summary

- In summary AD is a well-recognised entity and atopic eczema its commonest synonym.
- AD occurs in genetically predisposed individuals and in most cases is associated with asthma and/or hay fever
- The UK working party's diagnostic criteria remain the most thoroughly validated and easy to use in epidemiological studies. However, it is still possible that a better disease definition may be developed.
- There is an increase in the prevalence of atopic dermatitis and other atopic diseases. The peak prevalence of AD among infants and children.
- AD is more common in children and most of the sufferers have it in a mild form.
- The vast majority of AD cases were under the GPs care.
- Prevalence studies of AD based on a dermatologist's examination are largely lacking.
- There is no adequate explanation for the increasing prevalence of this condition.

1.2 Section 2: Aetiology and clinical features

1.2.1 Aetiology

The aetiology of atopic dermatitis to date is still unknown but it has been suggested that more than one factor, acting at the same time, may precipitate the disease. The relative importance of genetic, immunological, environmental, and local cutaneous factors in the aetiology of AD may vary between cases, a proposal that is supported by the variation in clinical presentation and prognosis. Atopic dermatitis may, therefore, represent a spectrum of disease process, with environmental factors dominating at one end of the spectrum and purely genetic factors at the other end (Rajka., 1960; Coleman, Trembath, Harper., 1997).

1.2.1.1 Genetic factors

Familial aggregation, suggesting a genetic predisposition, is a long established feature of atopy (Coca and Cooke., 1923). Family history of atopic disease is one of the recognised diagnostic criteria for AD (Hanifin and Rajka., 1980; Williams, *et al.*, 1994a). Schultz-Larsen *et al* (1986) demonstrated the central importance of genetic determinants. They reported a higher concordance of atopic dermatitis in monozygotic (77%) than dizygotic (15%) twins. The former finding and family history of atopy are strong indicators of the genetic basis of the disease (Schultz-Larsen, Holm, Henningsen., 1986). Diepgen and Blettner (1996) reported a higher odds ratio of atopic dermatitis between mothers and sibling than fathers and sibling. The familial aggregation between mother and child can be explained by the sharing of the same environment at home, or by intrauterine influences. They assumed that environmental factors would be shared more

between mother and child than father and child (Diepgen and Blettner., 1996).

Recent developments in molecular biology and genetics have led to the identification of a number of candidate genes, which are related to atopic diathesis or to increased IgE production. A study of allergic rhinitic or asthmatic families suggested that dominant inheritance of the IgE response was linked to a gene locus on chromosome 11q (Cookson, Sharp, Faux, Hopkin., 1989). However, in another study the authors were unable to detect or exclude linkage of atopic dermatitis to this gene (Coleman, Trembath, Harper., 1993). A finding that contrasted with a later study where the authors found that there was significant association of atopic dermatitis with beta subunit of the high affinity IgE receptors gene (Cox, Moffatt, Faux, *et al.*, 1998). In partial agreement with the Coleman's study (1993) and disagreement with Cox's study (1998) there was lack of linkage to chromosome 11q13 but linkage to chromosome 5q31, in a study in which Forrest *et al* identified the major locus that causes general predisposition to atopy at 5q31. They proposed that there are different genes, which in the presence of environmental factors determine how the atopy is expressed in form of eczema, asthma or rhinitis (Forrest, Dunn, Williamson, *et al.*, 1999).

In a recent review of the genetic studies of atopy and atopic dermatitis, Coleman *et al* concluded that atopy and atopic disorders occurs as result of multifactorial inheritance with interaction between genetic and environmental factors in which the exact contribution of each factor remains unclear (Coleman, Trembath, Harper., 1997). It can be concluded that genotype is an important risk factor for the development of AD. This may represent more than a single gene defect, varying from inheriting a high-risk gene pattern

where environmental factors do not play a major role. to a low risk genotype expressed under certain environmental conditions. Finally, Cookson concluded recently that with the availability of the complete sequencing of the human genome and the ability of looking at the expression of many genes at once, the identification of the responsible genes will be much easier (Cookson., 2001).

1.2.1.2 Environmental factors

While atopy has strong genetic determinants, still unrecognised factors in the environment can affect the occurrence of AD in genetically susceptible individuals. It is unlikely that genetic factors are solely responsible for the rapid change in the prevalence of AD (Williams., 1992). Geographical variation of AD in the UK in a similar pattern to hay fever cannot be explained in genetic terms alone (McNally, Williams, Phillips, Strachan., 2000). Also, children of black Caribbean origin born in London have been shown to be at higher risk of AD than their white counterparts (Williams, Pembroke, Forsdyke, *et al.*, 1995a). The former study suggested that environmental factors associated with development and possibly urbanisation were important in the aetiology of AD. Environmental factors may act during foetal life or during infancy.

Changes in the indoor climate as a result of central heating and double-glazing might for example, have increased children's exposure to house dust mite. Hide *et al* (1994) carried out an intervention study where they manipulated diet and the level of antigen exposure from house dust mite during gestation and early infancy in children at higher risk of developing atopic diseases. They found a significant reduction in the number of new cases of allergy than in the control group at the age of 2 years (Hide,

Matthews, Stevens, *et al.*, 1994). However, the literature provides little information about the nature of these factors, specifically whether these are allergic in nature such as exposure to new or higher concentrations of airborne or dietary antigens, or whether they are mainly physical such as soap or detergents.

1.2.1.3 Immunological factors

It is beyond the scope of this thesis to review or discuss the recent immunological findings, however an overview will be given. Increased IgE levels, eosinophilia, decreased CD8 suppressor/cytotoxic cell number and function, increased expression of CD23 on mononuclear cells, expansion of IL-4 and IL-5 Th2-type cells (now called type II T-cell response), decreased number of IFN-gamma-secreting Th1-type cells (now called type I T-cell response), increased serum sIL-2 receptors levels, increased serum eosinophilic cationic protein levels, and other immunological abnormalities observed suggest an abnormal immunoregulation in AD (reviewed in Leung., 1999). These all point out to the importance of the T-cell in AD pathophysiology and is supported by data from clinical trials that showed that therapies that inhibit T cells can ameliorate AD, for instance oral cyclosporin A (Harper, Ahmed, Barclay, *et al.*, 2000), topical tacrolimus FK506 (reviewed in Smith., 2000), and SDZ ASM 981 (Harper, Green, Scott, *et al.*, 2001).

Also, in relation to disturbed cellular immunity, atopic dermatitis patients are said to be more susceptible to viral infection especially molluscum contagiosum and herpes simplex (Hanifin and Lobitz., 1977b). It has been reported that atopic dermatitis patients have a lower sensitisation rate to dinitrochlorobenzene (DNCB) than unaffected people, but Uehara and Sawai (1989) have reported, from a longitudinal study, that the reduced response

was correlated with disease severity. Of the 20 patients who did not react to DNCB when they had extensive dermatitis, 18 reacted when their eczema was under control (Uehara and Sawai., 1989).

Staphylococcus aureus is the predominant skin microorganism in skin lesions of AD patients as well as in clinically normal skin without any sign of infection (Leyden, Marples, Kligman., 1974). There is experimental evidence that *S aureus* may lead to the development or exacerbation of AD through an immunological mechanism. IgE antibodies against *S aureus* have been detected in some patients (Walsh, Richards, Douglas, Blumenthal., 1981), and *S aureus* enhances the expression of CD23, the low-affinity receptor for IgE, on B lymphocytes and Langerhans cells (Neuber and Konig.,1992). Also, enterotoxins released by some staphylococci may function as superantigens which are potent T-cell stimulators that can join the MHC class II molecules on antigen presenting cells with lymphocytes bearing a T-cell receptor with a particular $v\beta$ region (McFadden, Nobel, Camp., 1993). Anti-staphylococcal therapy has improved AD lesions, a rationale that was based on a positive linear correlation between eczema activity and the degree of *S aureus* colonisation – the denser the colonisation the more severe the eczema (Williams, Gibson, Aitchison, *et al.*, 1990; Lever., 1996).

Airborne allergens such as house dust mite, and animal dander have been proposed as triggers of atopic dermatitis (Rajka., 1961). There is an increased population of house dust mite in houses with fitted carpets, which appears to be the most important aeroallergen. Many patients with AD have specific anti-IgE antibodies to house dust mite antigen, and in many cases the concentrations of these are higher than those to other allergens (Platts-Mills, Mitchell, *et al.*, 1983), implicating dust mites as the most important

aeroallergens. The concentration of house dust mite antigens detected in the beds of patients with AD was found to be parallel to the severity of the disease, which supports the hypothesis that mite antigens may have a role in the aetiology of AD (Beck and Korsgaard., 1989), although others could not demonstrate a correlation (Henderson, Kennedy, Thompson, Carswell., 1990). At present, the role of the house dust mite is still controversial. However, it has been reported, from a controlled trial of dust mite avoidance measures in the treatment of AD, that there is a significant decrease in symptoms and extent of rash. The authors could not identify those subjects who might benefit from such interference and suggested that such methods are needed generally in the management of AD (Tan, Weald, Strickland, Friedmann., 1996).

Finally, penetration of the mucosal surface by food allergens will lead to antigens reaching food specific IgE antibodies bound to mast cells. Mediators such as histamine, prostaglandin, and leukotrienes are released. Cytokines such as IL-4, IL-5, IL-6, and TNF-alpha may promote inflammation released by activated mast cells. Such cytokines are also produced by Th1 cells that act to enhance migration of lymphocytes to the area involved establishing a chronic inflammatory reaction. Therefore, elimination of the properly identified responsible food allergen from the diet in some patients might result in a reversal of these immunopathogenic mechanisms and might improve the patient's skin condition (Sampson., 1997). However there is little clear evidence that ingested allergens are specifically related to AD in more than a small group of patients. Food as a risk factor will be shown in more details in subheading 1.3.2.3.

1.2.1.4 Local cutaneous factors

Factors whether internal or external acting locally may contribute to occurrence and/or exacerbation of AD. Dry skin, white dermographism and facial pallor (physiological changes in the skin) are well-recognised features of AD (Hanifin and Rajka., 1980). Dry skin could be related to changes in epidermal water loss (Watanabe, Tagami, Horii, *et al.*, 1991), lipid fractions (Yamamoto, Serizawa, Ito, Sato., 1991), or delivery of lamellar bodies (Fartasch, Bassukas, Diepgen., 1992). Abnormal cutaneous responses to acetylcholine (Lobitz and Campbell., 1953) and histamine (Uehara., 1982) have been documented to play a role in AD aetiology.

Morren *et al* reviewed triggering factors for AD and concluded that low humidity, excessive exposure to soaps, hard water, wool, and disinfectants were associated with eczema exacerbation (Morren, Prezybilla, Bamelis, *et al.*, 1994).

It can be concluded that there is not enough evidence to differentiate whether the abnormalities of immune function and cutaneous physiology reported in patients with AD are primary genetic defects or secondary changes resulting from environmental influences. For example, the barrier defect may enhance penetration of allergens or irritants, and on the other hand inflammation resulting from immune responses may alter the barrier function.

1.2.2 Clinical features

The clinical features of AD include itching, macular erythema, lichenification, excoriation, dryness of the skin and secondary infection. These signs and symptoms and others seen in AD patients will be described in the following subheading.

1.2.2.1 Symptoms and signs

Erythema and pruritus are the earliest primary events and these tend to occur as the disease flares in an acute or subacute form. Follicular accentuation may be more obvious in black skin. Vesicles are more common in flares affecting palms and soles. Excoriation and lichenification are secondary features that arise as a result of scratching and rubbing respectively.

The morphology of lesions in AD may vary with oozing being common in infants and lichenification more frequent later in life. Dry skin is a well-recognised and common feature, but is not specific, for AD. It is more common in winter months. Hyperlinear palms and keratosis pilaris typically occur in ichthyosis vulgaris. The latter has been reported in 2-6% of patients with AD and features of AD are seen in about 50% of patients with ichthyosis vulgaris (Rajka., 1989a). *Staphylococcus* infections in the form of small follicular pustules, mostly on the extremities, are seen in AD patients, and lesions may be crusted and impetiginised in childhood (Hanifin and Rogge., 1977a). Kaposi's varicelliform eruption (eczema herpeticum) is the most serious viral complication of AD, which can be localised or generalised. It is important to mention that the occurrence and severity of herpes infection and eczema severity are not related. That means that a patient with mild eczema may still have severe herpetic infection (Lever., 1996).

Flexural dermatitis in areas such as the cubital and popliteal fossae is essential to the diagnosis of atopic dermatitis (Hanifin and Rajka., 1980; Williams, *et al.*, 1994a), however these areas may be involved in other skin diseases such as psoriasis. Nipple eczema is relatively uncommon but specific of atopic dermatitis, and cheilitis is common in patients with atopic dermatitis. Eyelid dermatitis can lead to epidermal thickening and Hertoghe's patch (patchy loss of eyebrows) because of chronic rubbing. Infraorbital fold (Dennie-Morgan) is a single or double crease in the lower eyelid found in 50-60% of AD patients and also found in non-atopics. Periorbital darkening is possibly caused by chronic oedema and inflammation with secondary hyperpigmentation. Cataract, keratoconus, and increased risk of retinal detachment are ophthalmologic features associated with AD. Pityriasis alba is a temporary patchy loss of pigment associated with mild eczematous changes and is more evident in coloured skin (Rajka., 1989a).

1.2.2.2 Clinical phases of atopic dermatitis

As mentioned earlier it has been accepted that AD has three different temporal phases or stages (Hill and Sulzberger., 1935).

1.2.2.2.1 Infantile Phase

The eczema during this phase affects the scalp, the cheeks, the front of the neck, the anogenital region, few areas on the trunk, and extensor surfaces of the extremities. The morphology ranges from dry, scaly and erythematous in mild cases to exudative, crusting and impetiginisation in severe cases, particularly in hospitalised patients.

1.2.2.2.2 Childhood Phase

From 18 months the distribution of lesions changes to involve flexural sites (neck, elbows, wrists, knees and ankles, possibly around the mouth and hands). The morphology also changes to become mainly papular with epidermal thickening as a result of itching and rubbing referred to as lichenification.

1.2.2.2.3 Adulthood phase

The distribution is similar to the previous phase with eczema being more marked on the face, the neck, the upper trunk, the upper limbs and the hands with dryness and lichenification predominating.

1.2.2.3 Associated conditions

Other atopic diseases such as asthma and hay fever are strongly associated with AD. Hay fever has a similar epidemiology to that of AD in the UK (Strachan., 1989). About 30% of children with AD may have asthma and/or hay fever, despite the fact that the age of onset is different in these diseases. Asthma and hay fever are also more common in children with severe AD (Queille-Roussel, Raynaud, Saurat., 1985), and conversely asthma has a poor prognostic effect on clearance of AD (Rystedt., 1985).

In addition to asthma and hay fever, other conditions such as increased susceptibility to mosquito bites, increased urinary tract infection, recurrent ear infection, and an increased tendency to headache have all been associated with AD. Also, it has been suggested that atopic patients have a lower risk of developing cancer. (Rajka., 1989a). Herpes simplex, viral warts, and dermatophyte infection may be associated with eczema (Lever., 1996). Nevertheless, atopic dermatitis should be excluded from other disease such

as infantile seborrhoeic dermatitis, allergic contact dermatitis, Hyper IgE syndrome, Wiskott-Aldrich syndrome, histiocytosis X, scabies, cutaneous lymphoma, and genodermatoses such as ataxia telangiectasia, phenylketonuria, and Netherton's syndrome (Holden and Parish., 1998).

1.2.3 Summary

- Genetic factors play a substantial role in the prevalence of atopic dermatitis but the pattern of inheritance remains unclear and complex.
- Immunological factors are clearly important, which is supported by clinical studies in which oral cyclosporin, topical tacrolimus, and topical ascomycin SDZ ASM 981 have proved to be effective treatments for AD.
- Environmental factors can exacerbate disease in genetically predisposed persons.
- Local factors may have substantial effects on disease exacerbation.
- The aetiology of this disease is still unknown, despite the recent discoveries at cytological level. It is clear that AD is of complex aetiology and the described factors (genetic, immunological, environmental, and/or local cutaneous) may act in different ways.
- The most important clinical features of AD are erythema, dry skin and flexural dermatitis.
- AD has different clinical phases with prominent extensor involvement in the infantile phase and marked flexural predilection in childhood and adulthood phases.
- Chronic dryness and lichenification are prominent features in childhood and adulthood phases.

1.3 Section 3: Risk factors

A risk can be defined as the probability of an individual developing a condition over a specified time and a risk factor is any characteristic associated with a disease, although this association does not necessarily have to be causal. There is limited information about factors that may associate with AD prevalence as well as little information about risk factors that may have an association with atopic dermatitis severity. The absence of any standard and easily administered instrument of severity assessment has hampered such studies. It is perhaps sensible to emphasise that the following reported factors are mainly related to disease prevalence and these factors do not necessarily have the same relationship with disease severity. More explicitly a factor can have a significant association with disease prevalence and at the same time have no association with disease severity. A risk factor can be intrinsic such as sex or age at onset; or extrinsic such as the social class, area of residence etc, or iatrogenic such as the use of topical steroids or systemic treatment.

1.3.1 Intrinsic factors

1.3.1.1 Sex

Atopic dermatitis affects both sexes with more females having the disease in adult life while more males are affected as children (Rajka., 1989a). Berth-Jones *et al* (1997) has shown that sex and risk of AD was not strongly associated (Berth-Jones, George, Graham-Brown., 1997). But the latter study looked at the prevalence of AD and not its severity. From an adult population, it has been reported that females had a higher risk of increased severity of persistent or recurring dermatitis (Rystedt., 1985), in which

number of sites was used to measure the severity of AD. The system used to assess disease severity in the former study has not been validated and data about the disease in the previous 20 years were collected retrospectively.

1.3.1.2 Ethnic group

Children, living in the UK, with a parent born in the West Indies or Africa are reported to be at greater risk of developing AD (Peters and Golding., 1987). However, these authors were not clear if this statistically significant difference was a consequence of the difference in using the term eczema by parents or physicians. To overcome the previous problem, Williams *et al* (1995a) conducted a study in south London to explore the differences in AD prevalence between ethnic groups, using a valid and reliable definition for AD. They reported that London-born black Caribbean children appeared to be at an increased risk of having atopic dermatitis (Williams, Pembroke, Forsdyke, *et al.*, 1995a). Another population-based study conducted in another area of the United Kingdom with a large Asian community failed to show any ethnic group differences in atopic dermatitis prevalence (Neame, Berth-Jones, Kurinczuk, Graham-Brown., 1995). All these studies looked at the risk of developing AD and not the course or severity of atopic dermatitis.

1.3.1.3 Age at onset

Age of onset is one of a number of minor criteria used to diagnose atopic dermatitis (Hanifin and Rajka., 1980; Williams, *et al.*, 1994a). Parents may not be motivated to report this factor because their child already has the disease, but age at onset has a potential role in exploring those factors that may have caused the disease. The impact of age of onset in AD has been reported, in most cases, from hospital-based studies (Rajka., 1989a; Queille-Roussel, Raynaud, Saurat., 1985). Two studies in which cases were

ascertained from the community (Aberg and Engstorm., 1990; Williams and Strachan., 1998) reported a later onset of disease compared with hospital based studies. Despite the discrepancies and limitation of the studies, it has been shown that atopic dermatitis starts before the age of 5 years in 70% of cases.

Queille-Roussel *et al* (1985) reported no association between age of onset and disease severity, a finding that conflicts with Rystedt (1985) who reported that early onset was associated with persistent lesions and poor healing. Both studies were based on hospital cases. Differences in the age of subjects at the time of follow up may explain this contrasting finding, 5.7 years in the Queille-Roussel's study (1985) and 44 years in Rystedt's study (1985). Although the former two studies mentioned the relationship between age of onset and disease severity, the authors did not use a valid systematic technique of severity assessment.

1.3.1.4 Age

It has been shown that AD improves with age and more than 50% of children outgrow their eczema (Williams and Strachan., 1998). A similar finding has been reported earlier from the UK in which AD patients had higher recovery rate. The author showed that atopic dermatitis patients have a tendency to spontaneous remission with age (Vickers., 1980). However, information about whether atopic dermatitis severity improves, deteriorates, or remains the same with increasing age does not exist.

1.3.1.5 Family size

Large family size was associated with decreased prevalence of AD (Golding and Peters., 1987). Rona *et al* (1997) reported that there was a negative relation between family size and wheezing or asthma, which may indicate a

protective effect of a number of children sharing an environment at a young age. The study was based on children aged 5 to 11 years in England and Scotland (Rona, Duran-Tauleria, Chinn., 1997). In another study based on adults aged 20 to 44 years, it was found that there was a negative association between family size and some symptoms suggestive of asthma 'hay fever and nasal allergies' and sensitisation to grass in young adults. However, no consistent significant association was found between family size and eczema, total IgE or sensitisation to other allergens (Jarvis, Chinn, Luczynska, Burney., 1997). In Denmark, low parity (small family size) was associated with an increased risk of developing AD (Olesen, *et al.*, 1997). None of these studies have investigated the effect of family size on disease severity.

1.3.1.6 Birth weight

Olesen and colleagues (1997) found that children with high birth weights for their sex and gestational age had an increased risk of developing AD. The study was based on children recruited from private dermatology clinics and dermatology and paediatric departments in Aarhus, Denmark (Olesen, *et al.*, 1997). On the other hand, very low birth weight (1500 grams or less) was associated with significantly lower point prevalence and 1-year lifetime prevalence of AD than term or near-term infants (Buhrer, Grimmer, Niggemann, Obladen., 1999). Although they mentioned an independent association between birth weight and AD prevalence, they did not report whether they had controlled for social class or not. Since social class could be a confounding factor because it has been reported that lower social classes have modest excess of low birth weight (Macfarlane A and Mugford

M. Birth counts. Statistics of pregnancy and child birth. London: Her Majesty's Stationery Office, 1984: 89-117: cited in David and Ewing.. 1988).

Olesen's (1997) and Buhrer's (1999) studies, however, contradict the finding from a community based-study in Leicester, UK, in which the authors reported that there were no significant differences in birth weight between children who developed AD and those who did not (Berth-Jones, *et al.*, 1997). The difference in study setting and different case definition may explain the incongruity of the finding. None of these studies looked at the relationships between birth weight and disease severity.

1.3.1.7 Gestational age

It was thought that increased duration of pregnancy may alter the development of the immune system in children (Bjorksten., 1999). Olesen and colleagues (1997) found an association between prolonged gestational age and later development of AD, while Berth-Jones *et al* (1997) showed that differences in gestational age were not associated with significant differences in eczema prevalence. The potential disparity between these two studies has been discussed previously. Both studies did not mention the association between gestational age and eczema severity.

1.3.1.8 Child's atopy

Atopic dermatitis, asthma and hay fever represent a triad of atopic diseases that are associated with each other. About 50% of children with atopic dermatitis developed asthma and 45% developed allergic rhinitis (Gustafsson, Sjoberg, Foucard., 2000). On the other hand children who have asthma and/or hay fever were reported to have a poorer prognosis and persistent disease (Rystedt., 1985). Queille-Roussel *et al* (1985) have reported from a prospective study that the duration of AD was shorter in pure

AD than when AD was associated with respiratory manifestations (asthma and asthmiform bronchitis). Although the Queille-Roussel's study (1985) examined the severity of AD in a hospital population for the first time, the system used has not been validated.

1.3.1.9 Parental Atopy

It has long been known that hereditary factors play an important role in the development of atopic dermatitis. A positive maternal history of eczema and/or a positive maternal history of asthma or hay fever are associated with an increased risk of developing eczema (Peters and Golding., 1987). In a study performed by Berth-Jones and others (1997), it was found that the most significant predictive factor for a child developing AD was a parental history of eczema. The same findings were reported from Denmark. In this study it was found that a family history of atopy was associated with an increased risk of developing AD (Olesen, *et al.*, 1997).

Fergusson et al (1982) showed that parental history of eczema was the strongest predictor of rates of childhood eczema but parental asthma was also related to childhood eczema (Fergusson, Horwood, Shannon., 1982). In another study in London, the authors found that maternal atopy was associated with a higher risk of developing infantile AD than paternal atopy. This finding clearly has significant value in the prediction of allergy in childhood, but whether this may be due to genetic or congenital factors or both is uncertain (Ruiz, Kemeny, Price., 1992). Uehara and Kimura in Japan, showed that a personal history of respiratory atopy in parents had no influence on the development of AD in the children. The authors also demonstrated that the prevalence of atopic dermatitis was significantly higher in the children whose parents had a personal history of AD (Uehara and

Kimura., 1993). From these studies, it is possible to conclude that children whose family had a positive history of atopic diseases were at increased risk of developing AD than those without atopic diseases. However, none of these studies investigated the association between a positive family history of atopic diseases and disease severity.

1.3.2 Extrinsic factors

1.3.2.1 Social class

The Registrar General's social class classification was introduced in 1911 and became standard classification in the UK. Social class was divided into six categories with solicitors and doctors being ranked in social class one and unskilled occupations, for example porters were ranked social class five. In between, there is social class 2 such as sale managers, social class 3-non manual such as shop assistants, social class 3-manual such as underground coalminers, and social class 4 such as bus conductors (Leete and Fox., 1977).

Social class I (father in one of higher professions) and the reported history of eczema have been associated. In parallel with the association with socio-economic status, children who had been said to have eczema were more likely to live in 'well-to-do' urban areas. Also, high maternal social class and a reported history of eczema were associated (Golding and Peters., 1987). In an attempt to identify independent predictors of eczema, the same authors found that higher parental-educational qualification was associated with an increased risk of developing eczema (Peters and Golding., 1987). In a comparison of parental reports of eczema with visible eczema recorded by medical officers during a detailed physical examination, Williams and others

found that eczema is more prevalent among British school children in social classes I and II than those in lower classes (Williams, Strachan, Hay., 1994d). A similar finding has been reported from a community-based study in which children born to unemployed fathers had a low tendency to develop AD: 4% of this group had AD (Berth-Jones, *et al.*, 1997). However, the association between social class and disease severity has not been reported in previous studies.

1.3.2.2 Area of residence

Area of residence could have a different impact on atopic dermatitis because of the difference in the environmental factors such car exhaust and water supply. There is a dramatic variation across regions in the UK, in the prevalence of AD, with the highest rate of eczema being reported in the south east (14.7%) and south west (13.8%), and the lowest rate in Scotland (8.3%), Wales (9.3%) and the north of England (9.5%). The differences were highly significant (Golding and Peters., 1987). The authors did not specify whether these areas were urban or rural. However, a study in Finland reported that the prevalence of AD was higher in urban areas and lowest in rural areas (Poysa, Korppi, Pietikainen, *et al.*, 1991). A similar high prevalence of asthma in the urban area was reported from South Africa. The authors reported that the prevalence of asthma in children was 3.17% in the urban area compared with 0.14% in the rural area (Van Niekerk, Weinberg, Shore, *et al.*, 1979). In eastern Germany the prevalence of atopic disease has increased since German unification; between 1991 and 1996 there was a significant increase in the prevalence of hay fever, atopic sensitisation, and eczema in 9 to 11 year old school children (Von Mutius, Weiland, Fritzsche, *et al.*, 1998). All these studies provide evidence for an increased prevalence of AD in the

urban areas. However there is currently very little information about the association of an urban environment with atopic dermatitis severity.

1.3.2.3 Food

Food can provoke both an allergic and a non-allergic reactions. The foods provoking most reactions were eggs, peanuts, milk, fish, soy, and wheat (Lever., 2001). It has been reported that exposure to an early diverse solid-food diet conveyed an increased risk of eczema (Fergusson, Horwood, Shannon., 1982). To decrease the risk of eczema, Atherton et al (1978) carried out study that involved cow's milk and egg exclusion diet. Atherton *et al* suggested, from this double-blind controlled crossover trial, that the value of diet in controlling atopic dermatitis is greater than previously believed (Atherton, Sewell, Soothill, Wells., 1978). However, it may be difficult for parents to discover such allergies: for example 3% of children aged 1 year have a positive prick test to milk, but by the age of 3 years, only 1% expressed such positive prick tests, representing an approximately 80% reduction in type I allergy (Host and Halken., 1990). In a cross-sectional and prospective study design, food allergy was detected in 65% of cases with mild to moderate AD. The authors concluded that the presence of food allergy is more likely to indicate a poor prognosis of severe AD and should be considered a potentially significant predictor of respiratory atopy (Guillet and Guillet., 1992).

Zeiger (1997) reviewed the role of prevention of food allergy and its affect on atopic disease and highlighted the need for more definitive data before any allergy prevention programmes are developed (Zeiger., 1997). Recently, David *et al* (2000) reviewed the data available about the effect of food on atopic dermatitis. They concluded that dietary elimination as an effective tool



in the management of AD has yet to be established by controlled trials and the evidence of long term benefit from dietary elimination does not exist (David, Patel, Ewing, Stanton., 2000). Therefore, the role of food remains a controversial issue that should be explored further.

1.3.2.4 Breast feeding

The effect of breastfeeding on the prevalence of atopic diseases remains a controversial issue. On one hand it has been shown that there is no evidence to suggest that breast feeding practices had any effect on rates of eczema (Fergusson, Horwood, Shannon., 1982; Peters and Golding., 1987). And on the other hand a study from Finland showed that 6 months of breastfeeding had prevented eczema during the first 3 years of life (Saarinen and Kajosaari., 1995). In agreement with the latter study Berth-Jones *et al* (1997) reported that exclusive breast-feeding was lower in children with AD than those without (28% versus 46%). However, the previous two studies' findings contradict with the findings reported from Japan which showed that breastfeeding elevated the risk of AD slightly, without statistical significance (Nakamura, Oki, Tanihara, *et al.*, 2000).

Breast-feeding did not appear to affect the risk of developing AD. However, none of the above studies reported the effect of breast-feeding on atopic dermatitis severity.

1.3.2.5 Wool

There is a tendency for itching and/or an eczematous reaction to develop after contact with irritants. Intolerance to wool has been included as a minor diagnostic criteria for AD (Hanifin and Rajka., 1980). It is not clear why patients with AD have irritable skin in general, and in particular to wool. It may be secondary to the dryness of their skin, which is possibly related to

disturbance of lipid content and hydration of the epidermis (Imokawa, Abe, Jin, *et al.*, 1991) To date there is no information about the effect of exposure to wool on disease severity.

1.3.3 Medical intervention

A wide range of effective remedies is used to treat flare-ups of atopic dermatitis. Emollients and topical steroids are the most commonly used therapies to control AD. Systemic therapy has been reported to be effective in controlling disease in severe cases not responding to conventional therapy. However, there is a lack of information about the effect of these therapies, whether topical or systemic, on the long-term outcome of disease. It is certainly true that many of the available remedies are effective in the short term and that patients may expect to achieve marked improvement in disease severity, but data on the long-term effect is still lacking. Medical intervention, nevertheless, could have a harmful effect despite the benefit effect. Unfortunately, the design implemented in the current study does not allow for the exploration of these effects because patients with severe disease are likely to be on treatment.

1.3.4 Summary of risk factors

- Child's atopy, black skin, first year of life, parental atopy and upper social classes were associated with an increase in the prevalence of AD.
- An increase in age or family size was associated with a decrease in the prevalence of AD.
- The relationships between AD prevalence and the following factors; breastfeeding, foods, sex, birth weight, and gestational age remain inconsistent and contrasting.
- Although it was documented that there was geographical variation in AD prevalence with higher prevalence in urban areas, none of the studies looked at the difference in disease severity between urban and rural areas. Comparing rural and urban populations may help in identifying factors that may affect disease severity and justify further studies investigating the effect of the urban environment on AD.

It is notable that most of the studies looked at the effect of the reviewed factors on disease expression and few studies mentioned the effect on disease severity. The lack of information about factors that may affect disease severity was, therefore, very recognisable and justify investigating the effect of these factors on disease severity in this study. Also, the majority of the studies were hospital-based and few community-based, and a hospital population is more likely to be biased towards severe cases and under-represent mild cases that form the bulk of AD.

1.4 Section 4: Disease severity assessment

1.4.1 General background

Data on the severity of illness are relevant to healthcare workers, pharmaceutical companies, the government, and most important, the patient. In everyday clinical practice physicians routinely make global assessments on patients' status and may make widely different decisions at different times, when presented with the same clinical data. Nonetheless, patient care relies on these global assessments. These informal judgements can be incorporated into standard systems to be used in clinical trials. In rheumatology, increasingly different indices have used individual endpoints to form a single outcome measure (Bombardier and Tugwell., 1982). This is often expressed in the form of scales, where the weighting and combining of each individual endpoint is made according to defined rules. Scales are helpful to simplify clinical information on individuals or groups, but fundamentally they are valuable tools to maximise the statistical power of a study design allowing the sample size to be small (Helewa, Goldsmith, Smythe., 1982). However, any instrument, index or technique designed to measure disease severity should be valid, reliable (reproducible), sensitive to change and acceptable for use by observer and patient (Streiner and Norman., 1995).

1.4.2 Disease severity measurement in dermatology

Easily administered standard instruments to measure disease severity for a range of dermatological disorders are quite limited and there is no single instrument that would be applicable to all inflammatory diseases or when

there is uncertainty about the diagnosis (Faust, Gonin, Farmer, *et al.*, 1997). At present assessments of disease severity in a patient with inflammatory skin disease are based on either a complex objective scale developed for clinical trials (e.g., Psoriasis Area Severity Index, Fredriksson, Pettersson., 1978; The assessment of acne vulgaris — the Leeds technique, Burke and Cunliffe., 1984), or global rating by a dermatologist into mild, moderate, or severe categories. There is a need for a scale that is reliable, quick, easy to use, and valid for categorising disease severity across a broad spectrum of skin diseases (Williams., 1997).

1.4.3 Atopic dermatitis severity measurement

Physicians most frequently assess this common skin disease in everyday clinical practice and clinical trials. It is necessary, therefore, to measure disease activity in a systematic way. However it is only recently that dermatologists have tried to develop a standardised system to assess AD severity. In 1989 the first scoring systems for AD severity assessment were published (Costa, Rilliet, Nicolet, Saurat., 1989; Rajka and Langeland., 1989). Hanifin (1989) in the same year published a proposal on how to grade AD in clinical research studies but this was not a tested scoring system (Hanifin., 1989). Since 1989 there has been an increasing interest in developing such systems. In total 7 systems to measure AD severity, shown in Table 2 in chronological order, have been published as full articles since 1989. Other scoring systems such as the Eczema Area and Severity Index (EASI) (Tofte, Graeber, Cherill, *et al.*, 1998) which was published in an abstract form have not been included in the table. Many other systems such as the Skin Intensity Score (SIS) and the Basic Clinical Scoring System (BCSS) were developed to measure disease severity in particular studies,

were also not included in Table 2. All these scoring systems, and many other scales using different combinations applied to assess disease severity in other studies, were thoroughly reviewed by Charman and Williams (2000b). They concluded that the SCORAD Index was the only scale for which validity, reliability, sensitivity to change, and acceptability has been tested (Charman and Williams., 2000b).

Table 2. AD Scoring systems where a full-article was published

Name of the Scale		Year of publication
Simple Scoring System	(SSS)	1989
Rajka and Langeland		1989
Atopic Dermatitis Area and Severity Index	(ADASI)	1991
SCORre Atopic Dermatitis	(SCORAD)	1993
Six Area Six Signs Atopic Dermatitis	(SASSAD)	1996
Assessment Measure for Atopic Dermatitis	(ADAM)	1999
Nottingham Eczema Severity Score	(NESS)	2000

1.4.3.1 The SCORAD Index

The SCORAD (**SCORE** Atopic **D**ermatitis) was developed by the European Task Force on Atopic Dermatitis as a disease-specific severity measure (European Task Force on Atopic Dermatitis., 1993). The SCORAD is composed of three parts. First; the extent of involvement using the rule of nine. Second; six intensity items (erythema, oozing/crusting, oedema/papulation, excoriation, lichenification and dryness), each one on a scale from 0 to 3 according to an atlas of reference photographs (0 = absent, 1 = mild, 2 = moderate and 3 = severe). These features were chosen because of their incidence, clinical importance and potential for variation. The area chosen must be representative (average intensity) for each item in a given patient as determined by the investigators, thus excluding one target area or the worst affected side (European Task Force on Atopic Dermatitis., 1993). Half point scoring is not recommended and the same area may be

chosen for 2 or more items. Third; subjective symptoms (pruritus and sleep loss), in the last 3 days/nights are assessed by the parents on a 0 to 10 visual analogue scale.

The SCORAD Index was the most suitable system to use in this study because it has proved to be applicable and useful in epidemiological studies (Schafer, Dockery, Kramer, *et al.*, 1997). Although SCORAD was the most tested instrument, it does have following shortcomings:

1. Using the rule of nines in assessment of the lesion extent has been shown to have very poor inter-observer agreement (Charman, Venn, Williams., 1999). Inter-observer variability can affect the reliability of the instrument, but has no effect on this study because the same observer will assess disease severity all the time.
2. It is a point severity measure and does not reflect disease fluctuation over the previous weeks or months.
3. It combines both subjective and objective scores, a feature which is considered to be a drawback against its validity.
4. There is some redundancy of information because of overlap between signs such as scaling and erythema; a drawback not only of the SCORAD, but of all other assessment systems.

1.4.3.2 Rajka and Langeland scoring system

The Rajka and Langeland system is based on clinical course, intensity, and extent of atopic dermatitis. The extent uses the rule of nines, the course from the history and the intensity from information about disturbance of night's sleep by itching. The broader categories (mild, moderate and severe) of this system, would make it more suitable in selection of patients entering a clinical trial rather than for detection of short-term change after intervention

(Rajka and Langeland., 1989b). There is no published data on the responsiveness of this scoring method to change and the lack of any reliability testing goes against the use of this system.

1.4.3.3 The Simple Scoring System (SSS)

The SSS is a simple technique that adds observer assessment of signs to patient's assessment of symptoms (Costa, Rilliet, Nicolet, Saurat., 1989). It consists of 10 severity criteria on a scale from 0 (no lesion at all) to 7 (extremely severe) giving a maximum score of 70, and ten topographic sites are used to assess the extent of disease in each area on a 0 to 3 scale (maximum 30). The most severely affected area was chosen for assessment with each criterion, giving a maximum total score of 100. Choosing the most severely affected area would make assessment quite difficult in a community-based study, in which most cases are mild. Although combining patient's (subjective) scores and observer's (objective) scores was considered to be a disadvantage of using this system, it may prove necessary to provide a comprehensive assessment of the atopic dermatitis status. However, in every-day practice collecting information about 20 parameters for each patient is impractical.

1.4.3.4 The Atopic Dermatitis Area and Severity Index (ADASI)

The ADASI is based on three colour codings (Green, Blue and Red) of diseased areas according to severity on a body scheme. Green; discrete erythema with or without some scaling, but no infiltration. Blue; erythema with some infiltration, more or less scaling. Red; marked erythema with infiltration, with or without scaling; or lichenification with or without excoriation, with or without superinfection. The extent of the coloured areas is evaluated by point counting and the AD severity calculated by mathematical equation (Bahmer,

Schafer, Schubert., 1991). There is no published data on reliability testing and the scheme is not as simple as it might first appear.

1.4.3.5 The Six Area, Six Sign Atopic Dermatitis (SASSAD)

The SASSAD score is obtained by grading six signs at six sites. The signs are erythema, exudation, excoriation, dryness, cracking, and lichenification, each on a scale of 0 to 3 (0 = absent, 1 = mild, 2 = moderate, and 3 = severe). Each of these six signs is evaluated at each of the following six sites; head and neck, arms, hands, trunk legs, and feet. The maximum score is 108 (Berth-Jones., 1996a). Subjective symptoms are measured separately using a visual analogue scale. The SASSAD was proposed mainly as a severity measure to quantify response to treatment in clinical trial, although it may have additional applications. The system might be expected to show a substantial inter-observer variation. Although the author mentioned in the original article that the SASSAD proved to be useful in a community-based epidemiological study (Berth-Jones., 1996a), there was no evidence from the published literature to support this statement. The SASSAD contained many of the clinical features assessed in the SCORAD but does not have any published data on reliability testing. Four of the six signs are used in the SCORAD (erythema, excoriation, lichenification, and dryness). It was concluded, therefore, the SCORAD would be better for use in assessing AD severity in this study than the SASSAD because of the availability of data on its validity, reliability and sensitivity to change.

1.4.3.6 Assessment Measure for Atopic Dermatitis (ADAM)

This scale involves an assessment of 6 body areas (face, arms, hands, legs, feet, and trunk) for lichenification, scale/dryness, erythema, and excoriation (scale of 0 to 3), and another 4 body areas (scalp, napkin area, head and

neck, and limbs) for the presence or absence of eczema. The scoring system was derived by a log transformation and complex mathematical mode (Charman, Varigos, Horne, Oberklaid., 1999a; Charman and Varigos 1999b). Again the complex calculation of the total score, lack of validity testing and the inclusion of similar items, made the SCORAD more suitable to use.

1.4.3.7 The Nottingham Eczema Severity Score (NESS)

The NESS is the most recent atopic dermatitis severity system designed to measure disease severity in epidemiological studies (Emerson, Charman, Williams., 2000). The NESS was based on the Rajka and Langeland scoring system described in 1989 (Rajka and Langeland., 1989b).

The eczema severity is measured by evaluating the three elements of clinical course, disease intensity and the extent of eczema examined. First; clinical course assessment by asking the parents about the total duration of the child's eczema in the last 12 months, with less than 6 weeks equal to one and more than 9 months equal to five. Second; clinical intensity assessment by asking the parents about the sleep loss due to itching or scratching over the last 12 months. Parents were given 5 options with no sleep disturbance on an average week equal to one and 6 or more nights equal to five. Third; the extent of eczema by examination. The system has avoided the rule of nines that Rajka has used by using a system of tick boxes. The body surface area was divided, according to clinical distribution, into 45 areas. Numbers of areas involved were ranked into 5 categories with 0-2 equal to one and more than 20 equal to five. The maximum score of the NESS was 15 and subjects can be divided into three categories mild (3-8), moderate (9-11), and severe (12-15) (Emerson, Charman, Williams., 2000).

Its development was tested on pre-school children aged 1 to 5 years. There was an exact agreement observed between the NESS and dermatologist assessment in 88% of cases, and between the NESS and the parental assessment of eczema in 75% of cases. Poor correlation was observed between the NESS and the Children's Life Quality Index (CLQI), which is designed to measure QOL in all childhood diseases and not just skin diseases. At the time of writing, the CLQI has not been published together with work on the development of the index with Professor Andrew Finlay (*personal communication with Dr Emerson*). A trend in using different steroid cream potency (62% of mild cases, 94% of moderate cases and 100% of severe cases) was observed, consistent with severity grades by the NESS. Initial use showed satisfactory results when employed as a tool for disease severity measurement in epidemiological studies. However, further validation studies were recommended by the authors (Emerson, Charman, Williams., 2000b), and the 12 months recall time would have made the use of this system not compatible with this study design.

1.4.4 Summary of disease severity assessment

- Systematic way of severity assessment is really needed for evaluating the outcome in clinical trials and everyday practice. However, the ideal standardised, valid, reliable, sensitive, and easy to use scoring system still does not exist.
- In dermatology there are attempts to develop standardised systems to assess disease severity such as the PASI score for psoriasis and the Leeds technique for acne.
- There are quite large number of scoring systems for atopic dermatitis severity, in which data on validity and reliability still lacking.
- The SCORAD Index is the most tested instrument but shows inter-observer variation.
- The SCORAD and SASSAD give wide scale ranges that probably are beneficial in assessing small changes in clinical trials.
- The SASSAD has been used in many clinical trials but data on reliability have yet to be published.
- The Nottingham Eczema Severity Score (NESS) seems to be easy to use in epidemiological studies. But further data on its validity and reproducibility are needed. The 12 months recall time may underestimate disease severity.
- The SCORAD Index was judged to be the most suitable system to use in this study because data were available on its validity and reliability. It also has been shown to be a practical tool in epidemiological study. It was therefore decided to use the SCORAD to assess atopic dermatitis severity in this study.

1.5 Section 5: Quality of life

1.5.1 Background

Quality of life (QOL) in broad terms includes all factors that have an impact on an individual life, but health-related QOL is more specifically confined to health aspects. Apprehension of the “quality” of human life is not new. Philosophers throughout history have questioned how life gains quality, but assessment of the QOL has received an increasing interest in the last 50 years from the health care perspective. Treatment of chronic disabling conditions such as rheumatoid arthritis has focussed attention of the western health and social care systems on this aspect of illness (Doward and McKenna., 1998). In addition, it is now well recognised that the personal impact of disease cannot be comprehensively portrayed by measures of disease level such as size of infarction, tumour load, and forced expiratory volume. Other personal factors such as pain, restricted mobility, and financial cost must also be involved in the evaluation. The outcome of recognising this term resulted in a new area of research called “health-related quality of life”. It evaluates different kinds of burden from disease, their change with treatment and their effect on personal life (Muldoon, Barger, Flory, Manuck., 1998).

With time, QOL has evolved from an arbitrary concept into a topic of scientific enquiry (Bech., 1992; Parmenter., 1994). The first publication using a QOL measure appeared in the 1960s and the term was introduced as a heading on MEDLINE in 1975 and accepted as a concept by Index Medicus in 1977 (Doward and McKenna., 1998). Since then, there has been a great increase in publications using the term and most of these are experimental in nature.

In many cases steps taken to measure QOL in quantitative rather than purely qualitative terms, include an attempt to validate a scale of measurement or to demonstrate the extent of success from a particular treatment. In cases such as heart transplants, the improvement in QOL is significant and any technique of measurement can easily demonstrate the benefits of the operation. However, in other treatment areas where the effect is marginal, it is frequently the way of measuring QOL rather than the treatment itself, which means using the appropriate instrument that is sensitive to recognise the change. Over the next one or two decades other scales will be developed to measure health and then may replace existing systems. Until then the results of the use of such techniques should be interpreted with caution.

In the Constitution of the World Health Organisation (WHO), health is defined as “a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity” (cited in: Finlay., 1997). QOL is a global concept that theoretically should involve all aspects of an individual’s life and has been defined by the WHO Quality of Life (WHOQOL) Group in 1993.

“QOL is defined as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationships to salient features of their environment”

(WHOQOL Group 1993, cited in: Bowling 1995)

However, in simple terms, good quality of life is present when ‘*the hopes of an individual are matched by experience*’ (Calman., 1984). QOL assessment should be made as comprehensive as possible by encompassing the psychological, social, occupational and physical impact of a disease. A quality of life instrument should also be valid, reliable, responsive to change, and acceptable. Acceptability indicates the extent to which different people

(e.g. child, parents, nurses, physicians and other health-care professionals) are willing to use an instrument. Reliability (reproducibility) means that the instrument has the ability to detect true differences between subjects and consistent scores under identical circumstances. Responsiveness refers to the ability of an instrument to detect meaningful change when it occurs. Validity means that the scale measures what it is intended to measure (Streiner and Norman., 1995). Because of the lack of a gold standard validity is usually measured by the construct validity, in which the scale will show a positive correlation with other scales used by different observers to assess, for example disease severity.

Health-related quality of life approaches have led to development of many generic instruments such as the Sickness Impact Profile (SIP) instrument (Bergner, Bobbitt, Kressel, *et al.*, 1976), and the Short-Form (SF-36) questionnaire (Ware and Sherbourne., 1992). The SIP was developed in the seventies as a generic measure of perceived health status. The aim was to describe the changes in a person's behaviour in response to sickness. The SIP has been revised later and the final version contains 136 items in 12 categories (Bergner, *et al* 1976; Bergner, Bobbitt, Carter, Gilson., 1981). The SF-36 is a generic measure of health status covering eight domains: physical functioning, body pain, role limitations due to physical health, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.

1.5.2 Measuring quality of life in dermatology

QOL in dermatology is estimated for both research and clinical use, and as an audit for political and financial purposes. Doctors and patients may have

differing views on assessing the impact of an illness on quality of life from their patients (Slevin, Plant, Lynch, Drinkwater, Gregory., 1988).

Some of the components of the generic health questionnaires may be redundant in assessing quality of life in skin disease. For example in atopic dermatitis, an instrument that does not contain a question about the effect of itching may underestimate the impact of the disease on patient's life. As it has been reported that sleep disruption in pre-schoolers with atopic eczema was the ultimate outcome of itching and scratching. It caused tiredness, irritability and reduced attitude to perform normally (Reid and Lewis-Jones.,1995). Such generic measures of QOL also do not include many of the salient factors known to be associated with skin diseases, which may respond to treatment.

Skin disease has always had a major negative impact on a patient's life, but it is only recently that this impact has been measured in the repeatable way in which the Psoriasis Disability Index (PDI) was used to measure disability caused by psoriasis (Finlay and Kelly., 1987). After 1987 there was a flourishing interest in developing instrument(s) that could measure QOL in dermatology. Several questionnaires were the outcome of this growing interest; the Acne Disability Index (ADI) (Motley and Finlay., 1989), the atopic Dermatitis Disability Index (ADDI) (Eun and Finlay., 1990), the Eczema Disability Index (EDI) (Salek, Finlay, Luscombe, *et al.*, 1993), the Dermatology Life Quality Index (DLQI) (Finlay and Khan., 1994), the Children's Dermatology Life Quality Index (CDQLI) (Lewis-Jones and Finlay., 1995), the Dermatology Quality Of Life Scales (DQOLS) (Morgan, McCreedy, Simpson, Hay., 1997) and the Dermatitis Family Impact (DFI) questionnaire (Lawson, Lewis-Jones, Finlay, *et al.*, 1998). The Infants' Dermatitis Quality of

Life Index (IDQL) has been developed recently by Lewis-Jones and others (2001) to assess quality of life in infants (Lewis-Jones, Finlay, Dykes., 2001). Badia *et al* (1999) from Spain used the Spanish version of the DLQI in patients with mild to moderate eczema and psoriasis treated with topical steroids. They indicated that the Spanish version of the DLQI (Badia, Mascaró, Lozano., 1999) was generally valid and reliable, similar to its English version (Finlay and Khan., 1994). In Sweden, investigators had used the DLQI and other instruments such as the SF-36 (Ware and Sherbourne., 1992) to assess quality of life in adult patients with atopic eczema and psoriasis attending the dermatology outpatient clinic at a University hospital. They confirmed that patients with skin disease have an impaired quality of life (Lundberg, Johannesson, Silverdahl, *et al.*, 1999). The DLQI was also translated into Danish and it has been reported that the translated version has showed satisfactory reliability and was a valid measure to assess the impact of skin disease on quality of life using subjects with different skin diseases from inpatients and outpatient dermatology clinic, and healthy volunteers as a control. They showed that hospitalised patients had greater impairment in quality of life than both outpatients and healthy controls. Atopic dermatitis and psoriasis patients expressed higher scores than patients suffering from other dermatological diseases (Zachariae, Zachariae C, Ibsen, *et al.*, 2000).

1.5.3 Measuring children's quality of life

Measuring QOL in children has many difficulties. It includes the changing ability of children to read and understand questions, variation in normal activities and the recognition of aspects of life at different ages. Adult measures were not suitable for use in children because of the differing

experiences and their interpretation (Feeny, Juniper, Ferrie, *et al.*, 1998). Another crucial problem is separating the parents' from the children's perception of the disease affecting the child. Nevertheless, children's QOL measurement has received very little attention from researchers in health-related QOL (Lindstrom and Eriksson., 1993).

Skin disease such as atopic dermatitis can lead to severe disability and handicap in children (Long, Funnell, Collard, Finlay., 1993). A systematic way to evaluate the effect of skin diseases on children's life was needed. Therefore the Children's Dermatology Life Quality Index CDLQI was developed to measure the impact of any skin disease on children's QOL over the previous 7 days. It consists of 10 questions about different aspects of the child's life (Lewis-Jones and Finlay., 1995). On the initial validation of the CDLQI, Lewis-Jones and Finlay (1995) reported a high mean score for eczema, psoriasis, and acne. They were more highly significant than scores for moles and naevi. They confirmed the huge impact of inflammatory disease and in particular atopic dermatitis on children's QOL (Lewis-Jones and Finlay., 1995). However, information gained from this study was from children attending the paediatric dermatology clinic and not from a community-based study.

Although the CDLQI was designed to measure children' quality of life, it has not got around the difficulties mentioned earlier, and the parents were allowed to help in completing the questionnaire. Parents may provide a different view from their children. It could also be a source of information bias as there may be two different subjects answering the questions.

1.5.4 Measuring quality of life in atopic dermatitis

In a chronic disease such as AD with partial or temporary improvements, a valid, reliable and comprehensive instrument is required to judge the treatment. The prevalence of AD has increased over the last three decades and has caused a major impact on health care services and individual patients (Herd, Tidman, Prescott, Hunter., 1996). Increased prevalence multiplied by major impact necessitated more research to quantify the magnitude of this non-life threatening but stressful disease on health services, and eventually, may justify redistributing the resources available for medical researches and services.

The first questionnaire used to measure the impact of eczema on quality of life was called the Atopic Dermatitis Disability Index (ADDI), which contained 11 questions that cover all aspects of atopic dermatitis disability (Eun and Finlay., 1990). The authors modified the Psoriasis Disability Index (PDI) (Finlay and Kelly., 1987) to measure the impact of adult atopic dermatitis on quality of life. Thereafter another questionnaire was developed to measure the impact of atopic dermatitis on adult patients. The questionnaire was named the Eczema Disability Index (EDI), which was an adapted version of the PDI (Finlay and Kelly., 1987). Using the EDI and the Sickness Impact Profile (Bergner, *et al.*, 1981) in a clinical trial the authors were able to show that cyclosporin greatly improved the quality of life in adult patients with AD (Salek, *et al.*, 1993). However, the EDI used in clinical trials has not been tested for validity and reproducibility.

In a dermatology-hospital based clinics throughout the UK, using the DQLI, Finlay (1996) measured the effect of severe adult atopic eczema on QOL. He confirmed the major impact of severe atopic dermatitis on an adult's QOL

(Finlay., 1996). Berth-Jones *et al* (1996b) used a locally derived questionnaire, not formally validated, to assess quality of life in children with severe atopic dermatitis from hospital populations. The scores showed dramatic improvement after treatment with oral cyclosporin (Berth-Jones, Finlay, Zaki, *et al.*, 1996b).

In an abstract publication, it has been shown that the CDLQI scores improved after an inpatient treatment of atopic dermatitis or psoriasis. The authors also showed that the mean CDLQI scores had significantly improved after treatment for acne (Lewis-Jones, Lawson, Hill, *et al.*, 1996).

In a community study, Herd *et al* (1997) have used the DLQI and the Patients' Generated Index (PGI) to assess disability caused by atopic dermatitis. The PGI was designed to assess the impact of a specific disease on aspects of patient's lives that they see relevant, in the mean time they can rate the extent of the impact and judge their treatment (Ruta, Garratt, Leng, *et al.*, 1994). The PGI has not been used in dermatological diseases before, but was used in patients with back pain and showed good reliability and validity. When the PGI was used to assess disability caused by eczema, there was a significant correlation between the PGI and an overall DLQI scores. The authors concluded that the PGI can be used to assess disability experienced by dermatological patients. But the analysis included adults (over 16 years old) with atopic dermatitis and all children with AD were excluded (Herd, Tidman, Ruta, Hunter., 1997). In Denmark, the Danish version of the DLQI was used to assess quality of life in adults with atopic dermatitis and showed a positive correlation between the DLQI and SCORAD scores (Linnet and Jemec., 1999).

1.5.5 The impact of childhood atopic dermatitis on the family

Parents have the legal obligation to make decisions on behalf of their children and it is therefore important to seek their views on their child's health status. Severe AD has been documented as having a major impact on the quality of life in adults (Finlay., 1996), but the literature provides scanty data about the effect of childhood AD on the family's life (Lawson, *et al.*, 1998). It has been shown that severe AD has a traumatising effect on the family's quality of life, and can be minimised by oral remedies such as cyclosporin (Berth-Jones, *et al.*, 1996b). However, the instrument used in the latter study has not been tested for validity. Daud *et al* (1993) had studied the psychological effects of atopic dermatitis, looking at the impact of AD on parental stress and parenting. The mothers of children with AD were significantly more likely to report being highly stressed about their child than controls (51% vs. 20% respectively). Global quality of parenting was judged to be lower in mothers of children with AD than controls. For instance, mothers tend to assent to their children's demands more often than controls (Daud, Garralda, David., 1993). Lewis-Jones *et al* (1998), in an abstract publication, have reported, from a community study, that childhood atopic dermatitis had affected their lives as well as their families' QOL and the quality of life scores were correlated to disease severity scores (Lewis-Jones, Finlay, Hill, Dykes., 1998). However, in the latter study, parents assessed disease severity in the children and completed the QOL questionnaires sent to them by post. Even so, critical examination of the effects of AD on families has been limited (O'Hare and Krowchuk., 1998).

1.5.6 The effects of atopic dermatitis on Health Care Costs

Despite the high incidence of skin diseases and the serious quality of life issues for sufferers, very little health economic work has been done in the field of dermatology. Atopic dermatitis is an ideal model for health economic analysis in dermatology. It has an early onset, chronic relapsing course, unknown aetiology, is quite often refractory to treatment, and finally may lead to alarming complications if not treated properly. Atopic dermatitis, therefore, can be an excellent example for measuring the effect of skin disease on quality of life and health economics, in which both patients and payers are affected. Nevertheless, few studies have been carried out on the economic impact of atopic dermatitis, in spite of the fact that it is a common disease and has caused a significant morbidity in children of all ages (Arikian, Einarson, Doyle., 1998).

Atopic dermatitis has been reported to be the most frequent diagnosis made in paediatric dermatology clinics and is the most common skin condition in children younger than 11 years old (Hanifin and Rajka., 1980).

In the UK, extrapolated total expenditure on atopic dermatitis was £465m per year and the annual cost per capita was £7.38. Selection bias could not be totally ruled out, but the data give some idea about the relevance of the problem. The study was carried out in a semi-rural general practice in Livingston, Scotland. All patients with AD (infants, children and adults) were included (Herd, Tidman, Prescott, Hunter., 1996). In Australia, Su *et al* (1997) investigated the impact of childhood atopic dermatitis on family QOL and its financial costs. They instituted a questionnaire designed by Stein and Riessman (1980) to determine the effects of a chronic illness on parents and families with conditions such as spina bifida, ventilator dependence and

behavioural disturbance. The questionnaire was based on four scales (1) financial burden; (2) familial/social impact; (3) personal strain; and (4) mastery of coping strategies implied by the family to master the illness (Stein and Riessman., 1980). They found that childhood atopic dermatitis has a huge impact on social, personal, emotional, and financial perspectives of families. The estimated annual cost for managing a mild, moderate, and severe case of eczema was 330, 818 and 1255 Australians dollars respectively (Su, Kemp, Varigos, Nolan., 1997). In Germany, the total cost of corticosteroids alone was approximately DM 450 million and the annual cost of treating AD to society including doctor's fees, and care in hospitals was DM 7 billion. Subjects were adults aged 17-55 years with atopic eczema (Gieler, Hohmann, Niemeier, *et al.*, 1999). Finally, a very recent study from Nottingham showed that the annual UK cost of AD in children between 1 and 5 years inclusive between 1995-96 was estimated to be 47 million British pounds (Emerson, Williams, Allen., 2001), implying the high financial burden to the UK economy.

1.5.7 Summary of quality of life

- Instruments designed to measure quality of life in general may not be valid in dermatological diseases. Finlay and colleagues (1987) developed the first formal health-related quality of life assessment in dermatology.
- It is quite clear from the review of the literature in this section that there is a very limited amount of data about the quality of life in dermatology generally. In particular, there is a lack of information from prospective community-based studies, where the vast majority of cases with AD.
- Scanty data are available about the relationships between QOL measures and disease severity parameters. Also, the relationship between changes in family and children's quality of life and changes in disease severity in children with atopic dermatitis has not been documented, especially from a community-based epidemiological study.
- The DFI and CDLQI have been shown to be reliable and valid instruments to measure QOL of the family and children respectively in hospital-based studies.
- This lack of information necessitates the need to document the impact of eczema on children and families' lives and then to justify the claims for more resources to carry out further research on this non-life threatening disease that did not have significant attention from the fund holders. In addition, it may provide some idea about the validity of QOL questionnaires used on assessing quality of life in the community, because they were all developed in a hospital based setting.

1.6 Section 6: Therapy, prognosis, and prevention

1.6.1 Therapy

1.6.1.1 General measures

Managing AD requires an adequate knowledge of its natural history. It is a chronic relapsing disease that is pruritic, easily irritated, chronically dry and characterised by episodes of inflammation. Patients are usually advised to avoid known irritants such as soap, wool fabrics, detergents, and occlusive fabric such as nylon. Patients should also avoid any work that involves frequent exposure to soaps, solvent detergents, or harsh chemicals. In some cases other triggering factors such as house dust mite should be avoided if possible. Bacterial, fungal, or viral infection can trigger AD and must be treated with the appropriate therapy when necessary. Oral acyclovir must be used when there is any suspicion of eczema herpeticum. Stress can exacerbate AD and patients with severe AD may benefit from psychological counselling. Dietary restriction in managing patients with refractory AD, not responding to conventional therapy, may be beneficial in a small selected group of patients, in particular children (Graham-Brown., 1998; Thestrup-Pedersen and Ring., 1999).

1.6.1.2 Topical therapy

Frequent bathing and regular application of moisturisers after bathing remain central steps in AD management. Patients should use soap substitutes such as aqueous cream and avoid using creams containing fragrances or preservatives. Wet wrapping can be used to treat dry skin and minimise skin

damage caused by scratching during the night. Coal tar or tar gels may be of limited benefit in AD (Graham-Brown., 1998).

Topical steroids remain amongst the most effective remedies available for the treatment of AD. Ointment should be used when the skin is dry and cream or lotion when it weeping or oozing. The strength of steroid can be adjusted according the site and severity of the lesions. Diluted topical steroids can be applied and then covered by wet wraps (wet wrapping) in patients who have more severe disease. Although several studies have reported their efficacy and safety in the management of AD, information on the long-term management can only be assumed. The lack of controlled data on long-term efficacy and safety of corticosteroids causes many dermatologists be wary of their extended use. Local and potential systematic side effects of topical steroids have led to researchers to study the effect of other topical remedies such as topical tacrolimus (FK506) that has shown promising results in the treatment of severe AD in adults and children. Local irritation is the most frequent side effect of tacrolimus, and relapse after stopping treatment has been reported. Information about the long term outcome are not available (reviewed in Smith., 2000). Harper and others (2001) have reported the first use of topical SDZ ASM 981 in children with atopic dermatitis (Harper, *et al.*, 2001), however it is not clear how these will contribute to the long-term management of severe AD.

1.6.1.3 Systemic treatment

Oral antihistamines, preferably sedative, are used to control itching and improve sleeping time of the patients in some cases. Patients with AD may benefit from short courses of oral antibiotics and those not responding to topical therapy can have a sustained benefit from short courses of

prednisolone. Chinese herbs have a recognised effect in controlling AD, but the cost and lack of defined ingredients make them unacceptable, although many patients find them beneficial. Other systemic treatments such as cyclosporin, azathioprine, methotrexate, and interferon-gamma, which have been shown to be effective in severe AD not responding to conventional therapy, can be used when the indication is justified (Sidbury and Hanifin., 2000).

Light therapy (UVA or UVB) is useful in patients who are resistant to other therapeutic modalities. Few patients have unexplained photosensitivity and cannot tolerate UV light. Photochemotherapy (PUVA) has been used to treat severe AD in children and adults and many show a sustained improvement. The carcinogenic effect of UV light limits its usage for longer times (Thestrup-Pedersen and Ring., 1999).

1.6.2 Prognosis

Atopic dermatitis typically first occurs at 6-8 weeks of age coinciding with a period of co-ordinated motor activity that allows scratching and rubbing to take place (Hill and Sulzberger., 1935). Early disease onset, severe early disease, concomitant asthma, and a family history of atopic dermatitis appear to be the strongest and most constant predictors of poor prognosis (Rystedt., 1985). Vickers followed up patients with AD for 20 years and found that the recurrence rate was less than 10%. However, the study included patients with infantile seborrhoeic dermatitis who potentially carry a good prognosis. He reported that patients with eczema that started during the second year of life and later with involvement of extensor surfaces had a worse prognosis (Vickers., 1980). A less favourable prognosis has been reported in children with juvenile onset (age less than 5 years) AD, in which about two-thirds of

children will continue to have symptoms into childhood (Musgrove and Morgan., 1976; Van Hecke and Leys., 1981). Linna *et al* (1992) reported that eczema had disappeared in 18% of children when they re-examined them 11-13 years later and in 65% the eczema persisted but with lesser severity (Linna, Kokkonen, Lahtela, Tammela., 1992).

From another long-term follow-up study of two groups of patients, one which had been hospitalised and a second group treated in an out-patient department, not less than 24 years previously. At the time of the follow-up examination 62% of the hospitalised group and 40% of an out-patients group still had active AD in a mild form (Rystedt., 1985). In a follow-up study carried out by Lammintausta *et al* (1991) in Turku, Finland, atopic subjects were re-examined after 20 years. These patients had been previously examined at the dermatology department when they were 12-16 years old. The investigators reported 20 years later that the majority of cases show moderate or mild disease; only 6% and 35% had severe and moderate AD respectively (Lammintausta, Kalimo, Raitala, Forsten., 1991).

A recent study from the UK reported a worse long-term prognosis than some previous studies had suggested with the apparent and short-term clearance rates of 53% and 65% respectively. The study used data from the National Child Development Study (NCDS), which has a longitudinal design and is truly unselected (Williams and Strachan., 1998) whereas the previous studies have used selected patients.

1.6.3 Prevention

1.6.3.1 Primary prevention

Primary prevention means a policy of preventing disease from happening for the first time in unaffected individuals. Factors operating early even in utero may have an effect on determining the prevalence/incidence of AD. If it were possible to identify risk factors that are accessible to public health manipulation, high-risk groups such as families with atopic diseases might benefit from an intervention study. It has been shown that there was significant reduction in the subsequent prevalence of AD after manipulation of diet and house dust mite in infants at high risk of atopic diseases (Arshad, Matthews, Gant, Hide., 1992; Hide, *et al.*, 1994). These intervention studies, when possible, should have a long term follow up period to make sure that the onset of atopic disease is not simply delayed.

1.6.3.2 Secondary prevention

Secondary prevention means the implementation of a policy to reduce disease activity in those with established disease. Identifying environmental factors that affect disease severity, exacerbation, or flare-ups and manipulating those accessible factors may help in preventing severe disease and eczema in remission from flare-up. This is supported by the evidence that the avoidance of irritating factors may help prevent exacerbation of AD (Rajka., 1989a). At our current state of knowledge of AD, this is a very important step in managing the disease. Keeping eczema in a mild and stable form that could lead to the patients having normal lives, and can be a rewarding goal.

The outcome of primary and secondary prevention needs to be assessed by patients as well as doctors. Relying on the latter in assessment of intermittent disease such as AD may exclude the input from many individuals who might benefit from simple measures such as information programmes on how to use emollients (McHenry and Williams., 1995).

1.6.4 Summary

- Identify any triggering factors and avoid when possible.
- Skin hydration and application of suitable moisturisers.
- Topical steroids still remain the main topical treatment of AD and topical tacrolimus and other immunomodulatory preparations show promising results.
- Always consider other systemic treatments including light therapy in severe cases not responding to conventional treatment.
- Atopic dermatitis has a relapsing course and about 50% of cases grow out of it.
- Prevention of atopic dermatitis could be an achievable task by better understanding of those factors that may have an effect on disease behaviour.

Although plenty of remedies are available to treat AD, none provide a cure and relapse rate is relatively high in most of these medicines. It is therefore important to know about those factors that may affect disease severity and thereafter lead to deterioration in the AD status. This would help in the implementation of prevention policy and make it an achievable task. The available treatments have their own limitations and knowing about these factors may help to rationalise drug usage and therefore decrease the relapse rate

1.7 Section 7: Hypothesis and Aims

1.7.1 General summary of introduction

There are five clear points that can be concluded from this brief introduction about atopic dermatitis:

1. The aetiology is unknown
2. There is no cure for the disease.
3. Very little information is available about factors that may affect disease severity.
4. The impact of AD on children and families' life and the relationships between disease severity and quality of life measurements have not been documented prospectively, especially from a community-based study where most cases present.
5. In most of the studies the design has been cross-sectional design and not longitudinal; a few used a prospective design.

For this reason this study focuses on a different aspect of the problem; not why it occurs but what makes it worse. Exploring factors that may have an effect on disease severity might help not only in a better understanding of the disease process but also in disease control and prevention. Factors such as diet and environment in general are possibly amenable to public health manipulation. Other factors such as early onset and area of residence may produce a better understanding of disease pathophysiology.

Documentation of the impact of disease on quality of life and its relation to disease severity is also necessary. Not only will this improve our understanding of individual attitudes, which are often strikingly different, it also relates these to economic and psychological aspects of the children's

and the family's life. Such information is also required to support the search for further resources in research and services.

1.7.2 What was the hypothesis?

This study concentrated on two aspects of atopic dermatitis; firstly by looking at factors that may have an effect on disease severity, and secondly by documenting the impact of childhood AD on quality of life.

Regarding the first aspect there was no prior hypothesis and the following statement justifies the implemented approach:

“Scientific design of experiments dictates that one should start with a clear hypothesis, and collect such information as will assist in the testing of that hypothesis. This obviously included the collection of any variables that may confound or interact with the basic data.

Such minimal designs are admirable in the field of randomised controlled trials or animal experiments. It is by no means obvious that they are ideal in observational epidemiological studies. There are two possible major reasons for mounting an epidemiological study. One is to confirm a hypothesis or a given set of preliminary findings. The other is to start with a blank canvas and ask the broad question of how does a particular disease vary in a given population – what factors are associated with increased or decreased risk”.

(Golding and Peters., 1987)

In view of the previously mentioned statement by Golding and Peters (1987), it was thought more sensible to initiate work from a broad base and ask different questions about the disease behaviour. However, in a sense, the study attempted to address a generalised hypothesis, which is, that those factors that affect the disease prevalence may or may not have the same effect on the disease severity. This broad non-specific approach was used because there is little information from the literature regarding factors influencing disease severity.

The second aspect was concerned with the documentation of quality of life and its relationship to disease severity scores. The hypotheses were: First: Does eczema have an impact on QOL (children and family)? and Second:

How do QOL scores correlate with disease severity? Thirdly the study has recognised that eczema varies over time and the impact of the disease has also been followed over time.

1.7.3 Aims

In summary, the general aims of the study were to:

- Determine risk factors that may affect atopic dermatitis severity over time.
- Document the impact of atopic dermatitis in children on themselves and their families' quality of life.
- Assess the relationships between atopic dermatitis severity scores and quality of life scores at a point in time and over time.

2 CHAPTER 2 METHODS AND SUBJECTS

2.1 Section 1: Ethics

The study received ethical approval by St Thomas' Hospital Research Ethics Committee for the London-based population and by Dyfed Powys Research Ethics Committee for the mid-Wales population. Preliminary parental consent to help with the study had been obtained by post, and at the time of examination another informed parental consent was obtained. Before signing the consent form, parents and children were asked if they had any questions about the study and they were told that they could withdraw from the study at any time.

The project has been registered with the Data Protection Registrar (**Application number: PX3885353**).

2.2 Section 2: Study design and subjects

2.2.1 Study design

A follow-up longitudinal study design was implemented in order to evaluate risk factors for AD severity and to document the impact of AD on the QOL over time. This design generally means a defined group followed over a period of time. In studying disease behaviour, an investigator might make use of observations of the outcomes of patients whose eczema may improve, flare up, or get worse under natural circumstances. However, “drop outs” are one of the disadvantages of this design. Subjects may move away or leave the study for other reasons, including death from causes other than the disease under investigation. Substantial losses to follow-up can affect the validity of the results, especially if the outcomes of subjects lost from the study differ from those who remain in the study (Barker and Rose., 1995).

This study included two populations recruited through general practices in a city population, South London (Lambeth, Southwark, Lewisham and Greenwich) and a rural community, mid Wales (Rhayader, Caersws and Newtown). The first area surveyed, South London, had the highest population density while the second area, Dyfed Powys, had the lowest population density in the UK. South London represents an urban environment and mid-Wales a rural environment. The three practices in mid Wales are in the middle of a rural area; those from the urban areas of mid Wales were excluded from the mailing list according to population density. Interview and clinical examination of subjects took place to time with March 1998, October 1998, March 1999 and October 1999 (Figure 1). The last follow-up period started in October 1999 after which no more new subjects were examined. To improve the follow-up rate, 17 children who did not turn up for many appointments (3) were contacted after this date and by March 2000 the study was stopped.

AD severity was assessed every 6 months by the same observer using the SCORAD Index (European Task Force on Atopic Dermatitis., 1993). The children's quality of life was assessed by the Children's Dermatology Life Quality Index (CDLQI) (Lewis-Jones and Finlay., 1995) and the family's quality of life by the Dermatitis Family Impact (DFI) questionnaire (Lawson, *et al.*, 1998). Quality of life, for children and families, was measured only at the two visits in 1999 (March and October 1999).

2.2.2 Questionnaire construction

2.2.2.1 Purpose

Standard and systematic methods of collecting information produce the ideal way of carrying out this research. The main purpose of constructing the questionnaire was to collect information about potential risk factors and confounders in a standardised way. Questionnaires are sometimes the only means of gathering information; thus their construction demands considerable thought, as with any other form of measurement in medicine (Fallowfield., 1995). However, the questions should be both valid and reliable, but unfortunately, a well validated and standardised measure was not available for this project. The studied population included children who may not have been able to answer or understand the questions, and even if they could have understood, the reliability of their answers would be debatable. On the other hand the perspectives of parents may differ markedly from those of their children. Nevertheless the recruitment and follow-up questionnaires were designed to be completed by the parents, in order to make a sensible comparison and statistical analysis of data of the same quality.

2.2.2.2 Questions about potential risk factors and confounders

After reviewing the literature and interviewing parents of patients with atopic dermatitis, 100 questions related to potential risk factors for severity and behaviour of disease were developed. The main aim of reviewing the literature was to collect the available information regarding these factors. However, there have been no systematic studies designed to identify factors that may affect atopic dermatitis severity in a community-based study. In

constructing the questionnaire, it was assumed that factors that have an effect on disease prevalence might have the same effect on disease severity, although this is not necessarily true. In addition questions about factors implicated in the published literature as potential contributors to the occurrence or severity of atopic dermatitis such as age of onset and ethnic group were also included. The questionnaire included an enquiry into environmental factors at home such as type of heating, presence of fitted carpet, and frequency of household and mattress vacuuming.

Identifying potential confounding factors is a crucial step that should be taken before carrying out research of this nature in order to make controlling for confounders during inclusion or later in the analysis an easier task (Barker and Rose., 1995). Well-known potential cofounders such as ethnic origin and social class were included in the questionnaire.

The longest recall time was encountered in questions about birth weight, gestational age, breast-feeding, atopy in the family, and grading the severity of eczema when it first started.

It was thought that the observer could not be blinded to exposure such as sex, area of residence, and ethnic group, which could be source of bias. It was therefore decided to ask parents in the questionnaire to grade their child's eczema on a 0 to 10 scale (0 no eczema and 10 the worst eczema the child has ever had). This grading was included in the preliminary questionnaire and then was positioned in question number 29 in the recruitment questionnaire (Appendix 6.2) and question number 17 in the follow up questionnaire (Appendix 6.3).

The preliminary questionnaire had 100 questions in 10 pages and the final questionnaire had 41 questions in 5 pages. Most of the response format was

on a categorical scale and few in a simple dichotomous assessment in the form of yes/no responses. Other response formats included 0 to 10 scale (questions 20, 29 and 39) and open-end responses (questions 4, 6, 7, and 41). Regarding answer choices (boxes), most of the questions had less than 7 boxes except the following questions in the recruitment questionnaire: 5 about child ethnic group (10 boxes), 19 about history of atopic diseases in the family (23 boxes) and 25 about age(s) when the child has been free of eczema (12 boxes).

2.2.2.3 Pilot study

The reliability and validity of a question may be improved by precise wording, avoiding ambiguous and technical terms, and by repeating the questions in a different fashion to stimulate recalls (Fallowfield., 1995). The aim of the pilot study was therefore to improve the validity and reliability of the questionnaire. However, it was not feasible to test it statistically. Testing the reproducibility would have required asking the parents to fill in the questionnaire more than once. It was not feasible to do this because parents were generally unwilling to attend another appointment.

Bearing in mind the ideal population would have been from general practice but at that time GPs agreement to help was awaited. It was decided to pilot this instrument on patients with active disease in a hospital outpatients department, who had a diagnosis of atopic dermatitis in the age range of the targeted population (5-10 years). The pilot took place at the St John's Institute of Dermatology outpatient department from May to July 1997.

First the permission of the consultant in charge was sought and then the permission of parents to complete the questionnaire was gained. They were asked to complete the questionnaire in its provisional form and were

requested to make comments on any questions. In total parents of six children agreed to complete the questionnaire of whom 4 were white and 2 black. The ages of children were 7, 5, 5, 9, 6, and 8 years. All parents taking part were able to read the questionnaire. Thereafter the questions were modified when there was ambiguity or confusion to improve their accuracy according to suggestion made by the parents. Piloting helped remove irrelevant questions, to rephrase any ambiguous questions, and to rearrange the questions in order to avoid positional bias.

2.2.2.4 Recruitment questionnaire

By the end of the pilot study, the questionnaire was ready in its final form (41 questions in 5 pages) and was deemed suitable for analysis by a statistician. The final form of the questionnaire used on recruitment is shown in Appendix 6.2.

2.2.2.5 Follow-up questionnaire

Collection of information regarding factors that may change over time such as frequency of topical steroid applications and severity assessment by the parents requires a standard form also. Thus the initial recruitment questionnaire was modified to collect information about events in the previous 6 months. Questions regarding factors that would not change during this time such as ethnic origin, breast-feeding and gestational age were removed. This reduced the list to 22 questions in 3 pages (see Appendix 6.3). This questionnaire was not piloted because the recall time only was modified without any change in content and answer format of each question.

2.2.3 Subjects' recruitment, examination and follow-up

2.2.3.1 Potential subjects and recruitment

The study was initiated by contacting GPs in south London and mid Wales in January 1997. GPs were told that access to patients' notes was not required for carrying out this study. Travel expenses would be refunded but subjects would not be offered any payment for their participation. The latter was implemented to avoid any selection bias. It was a longitudinal survey to collect information prospectively and events that happened in the past would be gathered by a questionnaire. What was required from the GP's was a list of potential patients and a place to examine them, if that was convenient for the surgery staff.

A copy of the detailed protocol, recruitment letters, and questionnaires were sent to the GPs who indicated their interest in helping with this study. They were asked to create a list of all patients under a diagnostic code of eczema or dermatitis in the age range from 5 to 10 years (DOB: 01/01/1988 to 31/12/1992). The age was restricted in the contents of homogeneity for a number of reasons: Firstly; eczema behaves differently from one age group to another, especially from a younger age group (under 4 years) to an older age group. Second; older patients might have different perspectives and interpretation of life. Patients in this age group were expected to have the same morphological signs of atopic dermatitis (Rajka., 1989a). Repeat prescriptions for emollients and/or topical steroids were also used by some of the GPs to supplement the list of potential patients for screening.

After receiving the patients' list, all parents of children were sent two letters: one approved by their GP asking for preliminary agreement. one from the investigator explaining the study. a one page questionnaire about the UK

diagnostic criteria (Appendix 6.1) and a stamped (first class) addressed envelope for their reply.

In November 1997 GPs number one and two, in south London, released the first list. Patients from this practice were contacted by post in January 1998 and those who responded were examined in March 1998. It took practices number three and four in south London another 3 months to release the list of potential patients. Meanwhile, the ethical approval for the rural area (mid Wales) was awaited.

In August 1998, the study has the approval by the Dyfed Powys Ethics Committee. After this, GPs number seven, eight, and nine, from the rural area, released a list of potential patients. These patients were contacted by post in August 1998 and those who agreed to help were examined by the observer in October of the same year as well as patients from practices number three and four. Ethical approval was necessary before contacting any subject.

In order to supplement the numbers of subjects in both areas an additional number of GPs were contacted in the urban and rural areas respectively. Of these, two GPs (GPs number five and six) in the urban area and one GP in the rural area agreed to help. GPs number five and six released the list of patients in January 1999. The patients were contacted by post immediately and those who responded were examined in March 1999. One GP from the rural area, who agreed to help, was unable to provide a list of patients before August 1999. It was, therefore, excluded.

In total, parents of 377 children in both areas were contacted by post. Of these 165 responded and 137 children were included in the study of which 40, 70, and 27 were recruited during March 98, October 98, and March 99

respectively. One hundred and twenty attended the last follow up in October 99.

2.2.3.2 Case definition

The UK diagnostic criteria, shown in Table 1, were used to define cases with AD. A one page questionnaire (Appendix 6.1) encompassing the UK working Party's diagnostic criteria for AD (Williams, *et al.*, 1994a; 1994b; 1994c) was sent to the parents by post with the recruitment letters. The one page questionnaire contained 6 questions; one about one major criterion, four about minor criteria of the UK diagnostic criteria, and one about a past history of eczema.

Feasibility issues were also considered in selecting this population. The subjects who responded but did not turn up for their recruitment appointments were excluded from the start. They were considered liable to be less motivated to join the study and therefore unlikely to continue participation.

2.2.3.3 Subjects' examination

2.2.3.3.1 Organising place to examine the children

Many patients lived near their doctor's surgery. To maximise the attendance rate, GP's and their practice manager were asked about room availability to examine children. In the rural area the doctor's surgery or a home visit were the only places available for examination. In the urban area some of the practices were unable to provide a room for examination. The dermatology out patient departments at Guy's and St Thomas' hospitals were the alternatives; in some cases a home visit was made.

2.2.3.3.2 Organising the appointments

Parents who agreed to help had provided their phone numbers. In a few cases a phone number were not available. Parents were contacted by phone and asked for the most convenient time, within the organised-specific time for examination with the practice, for them and their children to come for clinical assessment of their children. They were also asked about the preferable place for examination, e.g. doctor's surgery or at home. After arranging the appointments, a letter with a reminder of the date and place of examination was sent to the parents. The investigator performed all the arrangements.

2.2.3.3.3 Organising Travelling

The rural area in mid Wales is a remote area with limited public transport. Rhayader has no train station and very limited bus services. It was mandatory to travel between the three-targeted practices by car, which was cost-effective and time saving as well. It also, allowed the observer to make home visits to places where it was impossible to get to by public transport. Each patient required 45 minutes for examination during recruitment and 20 minutes at follow-up. The observer was based in London and this necessitated a stay in a hotel in mid Wales for two weeks on recruitment and one week on each follow-up. However, buses and trains were used for travelling in the urban area.

2.2.3.3.4 Clinical examination

The children's clinical examination took place in March 1998, October 1998, March 1999, and October 1999 (see Figure 1). All children were examined while wearing their underpants only in the presence of an adult guardian. Children were free to refuse examination regardless of parental consent. A

previously trained observer carried out the examination and severity assessments at all the times. At the same time as the severity assessment, the presence of visible flexural dermatitis, the only sign in the UK diagnostic criteria for AD, was documented according the published protocol (Williams, Forsdyke, Boodoo, *et al.*, 1995b). Children were examined in the same season, during spring and autumn, 6 months apart. All parents were able to read the recruitment and follow-up questionnaires, and the observer remained blind to the results of the questionnaire. Travel expenses were refunded to the parents on showing a receipt.

2.2.3.4 Subjects' follow-up

Parents attending for the recruitment visit were contacted by telephone 6 months later to arrange a suitable time to examine their children. After arranging a convenient time for parents and children, a letter was sent to confirm the time and place of examination. Parents were asked again to fill in the follow up questionnaire (Appendix 6.3) and at the same time the same investigator evaluated eczema severity in the children. Examination of children took place in the same location as at recruitment and a home visit was always an option. The same process was repeated every 6 months, up to 4 times for some subjects. Children and family's quality of life was assessed on two visits during 1999.

Figure 1. Diagram for the clinical examination and follow-up dates

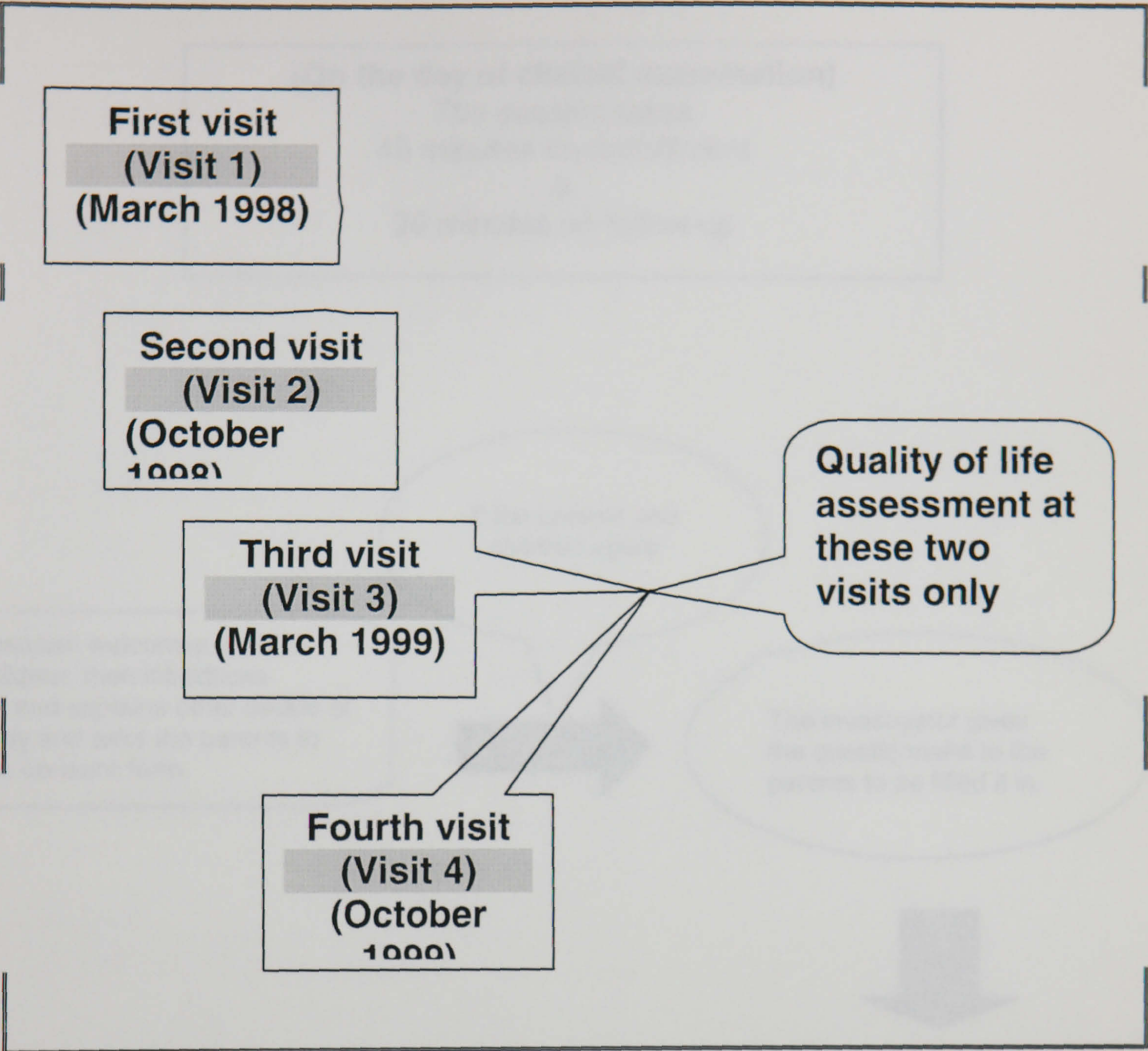


Figure 2. On the day of clinical examination of the child

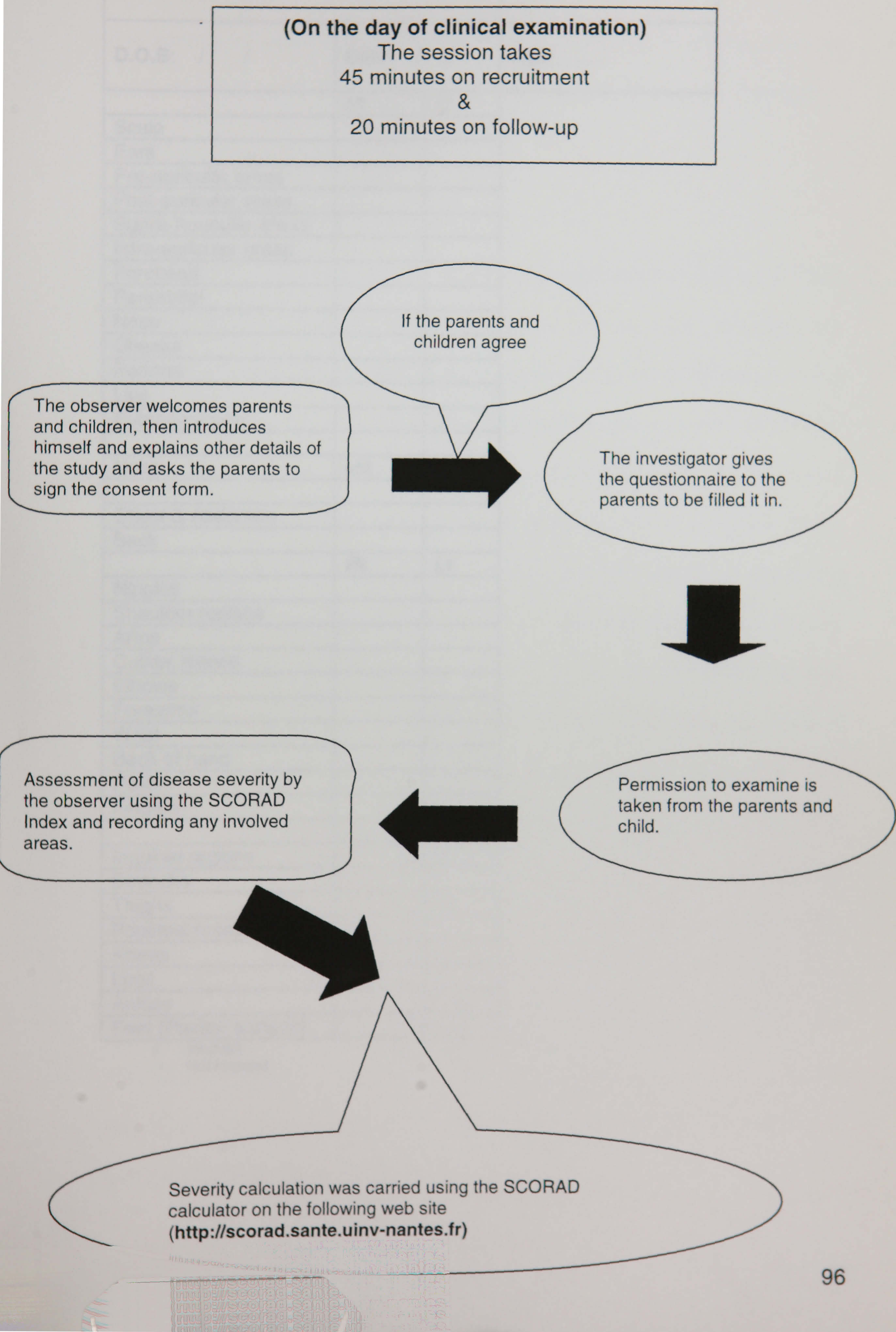


Table 3. Sheet for documentation of site involvement

Name:.....		QAD	
D.O.B: / /	Date: / /		Age:
	Rt	Lt	
Scalp			
Ears			
Pre-auricular areas			
Post-auricular areas			
Supra-Auricular areas			
Infra-auricular areas			
Forehead			
Periorbital			
Nose			
Cheeks			
Perioral			
Lips			
Submandibular			
Neck	ant	post	
Chest & Abdomen			
Back			
	Rt	Lt	
Nipples			
Shoulder regions			
Arms			
Cubital fossae			
Elbows			
Forearms			
Wrist			
Back of hand			
Palm			
Fingers			
Inguinal regions			
Buttocks			
Thighs			
Popliteal fossae			
Knees			
Legs			
Ankles			
Feet (Plantar surface)			

/ Involved
- Not involved

2.3 Section 3: Assessment of atopic dermatitis severity

The severity of atopic dermatitis in children was assessed by the observer using the SCORAD Index (European Task Force on Atopic Dermatitis., 1993).

2.3.1 The SCORAD Index

The SCORAD Index was chosen to assess disease severity because it was proved to be a practical tool in epidemiological studies. When the need is a detection of subtle modification in the severity of AD, as in follow-up of the progression of AD, a more elaborate scoring system such as the SCORAD is more appropriate (Sprickelman, Tupker, van Aalderen, *et al.*, 1997). It was also the most tested instrument available at the time of starting the study. Although patients generally over 7 years may well be capable of answering appropriately, children less than 7 years old might have been unable to read or understand the questions, thus parents exclusively answered the two questions to ensure that data had the same quality. The maximum score of the SCORAD is 103 and after exclusion of the dryness score, 92.5. This yields an atopic dermatitis severity score, which is a continuous variable. In the analysis of some factors such as family quality of life, the parents' scores were excluded and only the Objective SCORAD was used on its own (Kunz, Oranje, Labreze, *et al.*, 1997). The SCORAD-D will be used to refer to this form of modified SCORAD (maximum score of SCORAD-D is 72.5). The proposed evaluation sheet takes about 10 minutes to fill in for a trained individual. See the guidelines in how to use the SCORAD in Appendix 6.4 and the SCORAD sheet in Figure 3.

2.3.2 Training on how to use the SCORAD

The SCORAD is a scoring system to assess the severity of AD. Lack of experience with the instrument used in research is a source of bias and this could affect the result of the study. To minimise this, the investigator (observer) was trained on how to use SCORAD according to the practical guide in a SCORAD CD ROM (Stalder., 1995). Further information and automatic calculation of the SCORAD are available at the following website (<http://scorad.sante.uinv-nantes.fr>).

Training was achieved by practising the SCORAD on patients with AD from the outpatient's department. Permission from the patients' parents and the responsible doctor was first sought. Full examination of the child and recording of the extent of involvement using the rule of nine was applied. The six intensity items (clinical signs) were evaluated on a scale from 0 to 3 according to reference photographs. Dryness was assessed during a training session, because patients often do not apply cream before visiting their doctor. Parents were asked to assess the subjective symptoms in the last 3 days/nights on a 0 to 10 visual analogue scale.

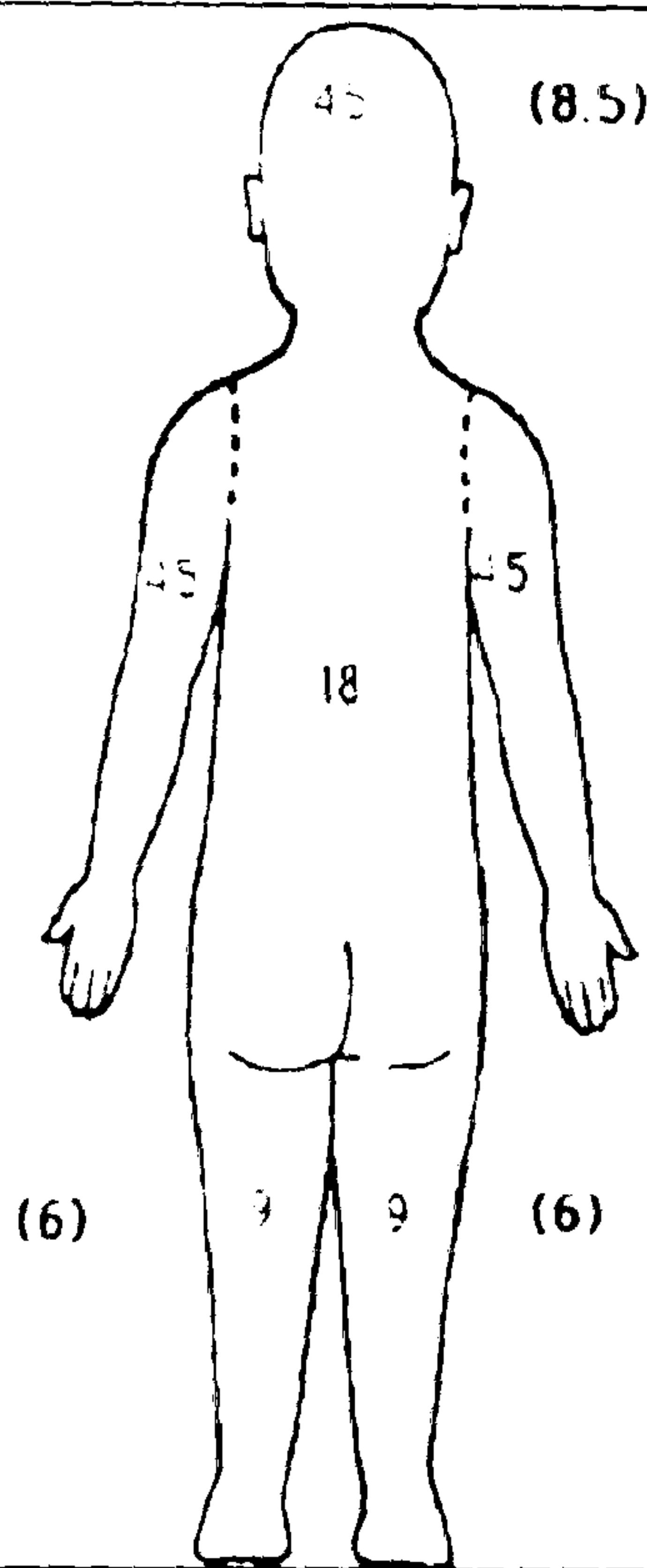
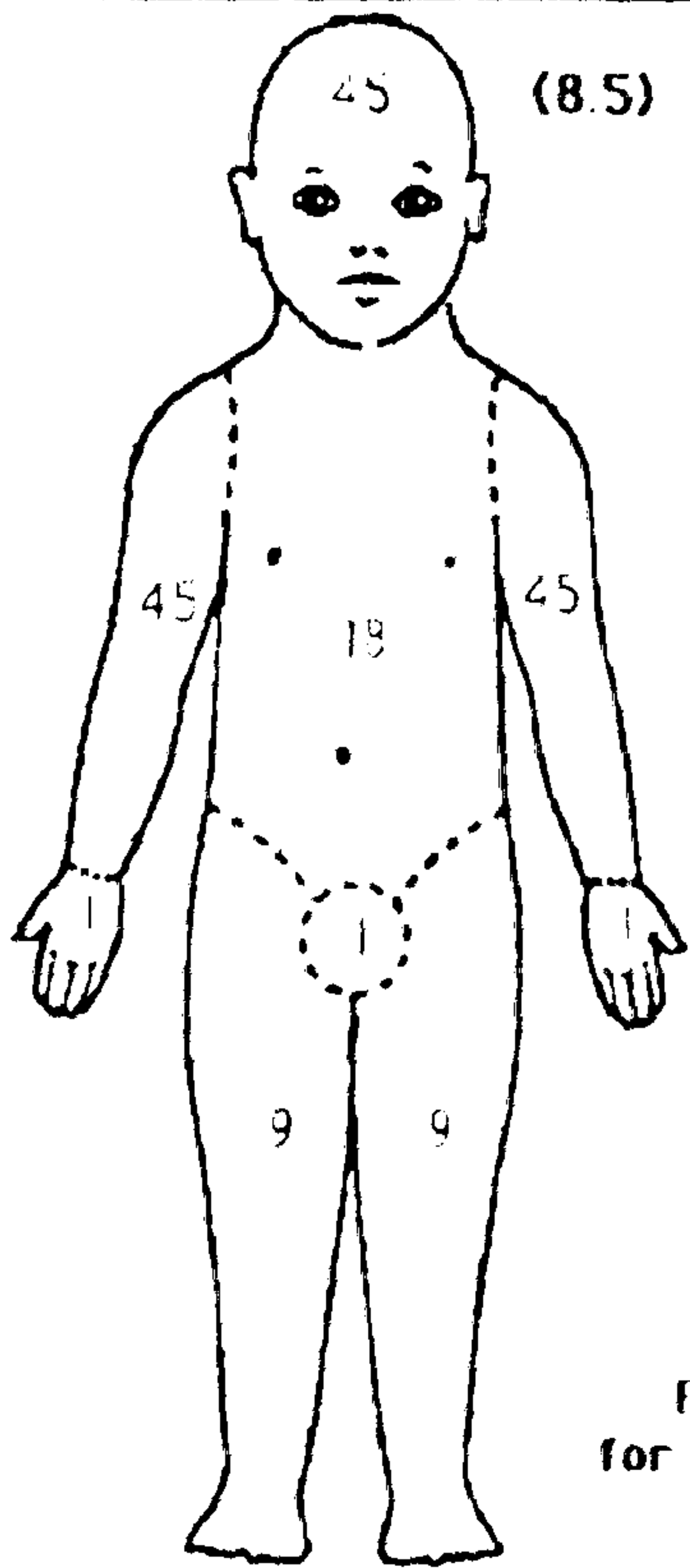
During training the minimum and maximum values obtained were 7.5 and 71.2 respectively. These values provided an adequate range of the variation in severity of the disease. Thus, the investigator was able to practice this scoring system on patients with varying degrees of severity with the aim of reducing the potential for observer bias (measurement bias). In the meantime the observer gained experience in assessing flexural dermatitis, the only clinical sign in the UK diagnostic criteria (Williams, *et al.*, 1994a).

SCORAD
EUROPEAN TASK FORCE
ON ATOPIC DERMATITIS

Last Name First Name
Date of Birth: DD/MM/YY
Date of Visit:

INSTITUTION
PHYSICIAN

Topical Steroid used:
Potency (brand name)
Amount / Month
Number of flares / Month



Figures in parenthesis
for children under two years

A: EXTENT Please indicate the area involved

B: INTENSITY

CRITERIA	INTENSITY
Erythema	
Edema/Papulation	
Oozing/crust	
Excoriation	
Lichenification	
Dryness *	

MEANS OF CALCULATION
INTENSITY ITEMS
(average representative area)
0= absence
1= mild
2= moderate
3= severe
* Dryness is evaluated
on uninvolved areas

C: SUBJECTIVE SYMPTOMS
PRURITUS+SLEEP LOSS

SCORAD $A/5 + 7B/2 + C$

Visual analog scale
(average for the last
3 days or nights)

PRURITUS (0 to 10) 0
SLEEP LOSS (0 to 10) 10

TREATMENT:
REMARKS:

Figure 3. SCORAD-index system

2.4 Section 4: Assessment of quality of life

Quality of life in children and their family were quantified by two different questionnaires. The contents of these two questionnaires will be explained separately. An ideal use of quality of life measures should be carried out at two key times to provide for example information before and after treatment. If it takes place too frequently, patients lose interest and become less careful, which may lead to loss of accuracy (Finlay.,1997). However, in this study, there is no active interference and it was decided that measuring quality of life at two points would provide the information needed to document the impact of AD on quality of life at a point in time and over time.

2.4.1 Family's quality of life

The parents attending visit 3 (March 1999) were asked to complete the Dermatitis Family Impact (DFI) questionnaire (Lawson, *et al.*, 1998) and then again 6 months later (October 1999), to assess the impact of atopic dermatitis on the family. The DFI, shown in Figure 4, was developed by Lawson *et al* as a disease-specific measure. It is a one-page questionnaire that measures how much atopic dermatitis in children has affected the life of the family over the previous 7 days. It consists of 10 items; house work, food preparation, sleep of others in the family, leisure activities such as swimming, time spent on shopping, cost related to treatment or clothes, causing tiredness or exhaustion, emotional distress, relationships in the family, and the impact of helping with treatment on the main carer's life (Lawson, *et al.*, 1998), see Figure 4.

Each question has four answers: 'not at all=0', 'a little =1', 'a lot =2', and 'very much=3'. The overall summary score aggregates the score of each item and

ranges between 0 (the best score) and 30 (the worst score). That is, the higher the score, the poorer the quality of life for the family. Parents have completed the DFI questionnaire at the same time as the children's eczema severity was assessed.

2.4.2 Children's quality of life

Unfortunately, a system that is designed to allow children to assess the impact of eczema on their quality of life without the help of their parents was not available. It was, therefore, decided to use the CDLQI, shown in Figure 5, in this study with the restriction that parents were not allowed to help in completion of the CDLQI. The children were asked to complete the CDLQI at first quality of life assessment visit (March 1999) and then again after 6 months (October 1999), to assess the impact of having atopic dermatitis on their quality of life.

The questionnaire was developed by Lewis-Jones and Finlay (1995) as speciality-specific one-page questionnaire to measure the impact of any dermatological disease on children's quality of life over the previous 7 days and was chosen because it was potentially of value in measuring the impact of the same skin disease in varied subjects relative to each other (Lewis-Jones and Finlay 1995). It consists of 10 items about different aspects of life: symptoms and feeling (questions 1 and 2), leisure activities (questions 4, 5 and 6), school or holidays (question number 7), personal relationship (questions 3 and 8), sleep (question number 9) and treatment (question number 10). Each question of the CDLQI has four answers (not at all = 0, only a little = 1, quite a lot = 2, or very much = 3). The sum of the 10 question scores forms the total score of CDLQI. The maximum score is 30 (the worst

score) and minimum is 0 (the best score). The lower the score, the less the impact on the child's life.

The targeted population contained children age 5 to 10 years, and some of them may not be able to complete the questionnaire on their own. However, parents and children were told that the child must complete the questionnaire without the help of anybody. Any child who received any help from his/her parents in completing the CDLQI was excluded from the analysis. The investigator had made the decision to exclude those who received help after the subject had left the examination room immediately to avoid any potential observer bias. That was done for the following reasons. First; this hopefully will reflect the child's own view of the disease and not that of his/her parents. Second; to ensure data of the same quality. Third; this restriction may give an idea about the applicability of the CDLQI in this specific age group, despite the fact that the CDLQI was designed to be completed by the child, with the help of his/her parent. However, a comment on how this restriction may have influenced conclusion from the data is discussed in section **4.3.2.1**.

All these questionnaires (CDLQI and DFI) were suitable and tested questionnaires to quantify the impact of eczema on children and families' life respectively. Despite evidence, that there are no published data on the validity of these instruments from a community based-study (except one study published in an abstract form; Lewis-Jones, *et al.*, 1998). Otherwise all the information was from hospital based-studies.

Family impact of childhood eczema questionnaire

Child's Name: _____ Mother/Father/Carer _____ Date: _____ Score

The aim of this questionnaire is to measure how much your child's skin problem has affected you and your family **OVER THE LAST WEEK**. Please tick ✓ one box for each question.

- | | | | |
|-----|--|------------|--------------------------|
| 1. | Over the <u>last week</u> , how much effect has your child having eczema had on housework, e.g. washing, cleaning. | Very much | <input type="checkbox"/> |
| | | A lot | <input type="checkbox"/> |
| | | A little | <input type="checkbox"/> |
| | | Not at all | <input type="checkbox"/> |
| 2. | Over the <u>last week</u> , how much effect has your child having eczema had on food preparation and feeding. | Very much | <input type="checkbox"/> |
| | | A lot | <input type="checkbox"/> |
| | | A little | <input type="checkbox"/> |
| | | Not at all | <input type="checkbox"/> |
| 3. | Over the <u>last week</u> , how much effect has your child having eczema had on the sleep of others in the family. | Very much | <input type="checkbox"/> |
| | | A lot | <input type="checkbox"/> |
| | | A little | <input type="checkbox"/> |
| | | Not at all | <input type="checkbox"/> |
| 4. | Over the <u>last week</u> , how much effect has your child having eczema had on family leisure activities, eg swimming. | Very much | <input type="checkbox"/> |
| | | A lot | <input type="checkbox"/> |
| | | A little | <input type="checkbox"/> |
| | | Not at all | <input type="checkbox"/> |
| 5. | Over the <u>last week</u> , how much effect has your child having eczema had on time spent on shopping for the family. | Very much | <input type="checkbox"/> |
| | | A lot | <input type="checkbox"/> |
| | | A little | <input type="checkbox"/> |
| | | Not at all | <input type="checkbox"/> |
| 6. | Over the <u>last week</u> , how much effect has your child having eczema had on your expenditure, eg costs related to treatment, clothes, etc. | Very much | <input type="checkbox"/> |
| | | A lot | <input type="checkbox"/> |
| | | A little | <input type="checkbox"/> |
| | | Not at all | <input type="checkbox"/> |
| 7. | Over the <u>last week</u> , how much effect has your child having eczema had on causing tiredness or exhaustion in your child's parents/carers. | Very much | <input type="checkbox"/> |
| | | A lot | <input type="checkbox"/> |
| | | A little | <input type="checkbox"/> |
| | | Not at all | <input type="checkbox"/> |
| 8. | Over the <u>last week</u> , how much effect has your child having eczema had on causing emotional distress such as depression, frustration or guilt in your child's parents/carers. | Very much | <input type="checkbox"/> |
| | | A lot | <input type="checkbox"/> |
| | | A little | <input type="checkbox"/> |
| | | Not at all | <input type="checkbox"/> |
| 9. | Over the <u>last week</u> , how much effect has your child having eczema had on relationships between the main carer and partner or between the main carer and other children in the family. | Very much | <input type="checkbox"/> |
| | | A lot | <input type="checkbox"/> |
| | | A little | <input type="checkbox"/> |
| | | Not at all | <input type="checkbox"/> |
| 10. | Over the <u>last week</u> , how much effect has helping with your child's treatment had on the main carer's life. | Very much | <input type="checkbox"/> |
| | | A lot | <input type="checkbox"/> |
| | | A little | <input type="checkbox"/> |
| | | Not at all | <input type="checkbox"/> |

Figure 4. The DFI questionnaire

Permission to copy and use the CDLQI and DFI was obtained from Professor Andrew Finlay and Dr Sue Lewis-Jones

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital No:
Name:
Age:
Address:

Diagnosis:

Date:

CDLQI
SCORE:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1. Over the last week, how itchy, "scratchy", sore or painful has your skin been?

Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

2. Over the last week, how embarrassed or self conscious, upset or sad have you been because of your skin?

Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

3. Over the last week, how much has your skin affected your friendships?

Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

4. Over the last week, how much have you changed or worn different or special clothes/shoes because of your skin?

Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

5. Over the last week, how much has your skin trouble affected going out, playing, or doing hobbies?

Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

6. Over the last week, how much have you avoided swimming or other sports because of your skin trouble?

Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

7.

Last week, was it school time? ✓

OR

was it holiday time? ✓

→
If school time: Over the last week, how much did your skin affect your school work?

→
If holiday time: How much over the last week, has your skin problem interfered with your enjoyment of the holiday?

Prevented school
Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

8. Over the last week, how much trouble have you had because of your skin with other people calling you names, teasing, bullying, asking questions or avoiding you?

Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

9. Over the last week, how much has your sleep been affected by your skin problem?

Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

10. Over the last week, how much of a problem has the treatment for your skin been?

Very much
Quite a lot
Only a little
Not at all

☐
☐
☐
☐

Please check that you have answered EVERY question. Thank you.

Figure 5. The CDLQI questionnaire

Permission to copy and use the CDLQI and DFI was obtained from Professor Andrew Finlay and Dr Sue Lewis-Jones

2.5 Section 5: Analysis strategy

2.5.1 Sample size calculation

One of the principal factors which influences the standard error (SE), and therefore the width of the confidence interval, is the sample size: generally, the larger the sample, the smaller the SE, and thus the narrower will be the confidence interval (Barker and Rose., 1995).

A statistician helped to calculate the sample size required for studying the risk factors for atopic dermatitis using the *Stata* software (Stata corp. 1999). Standard deviation (SD) of SCORAD was taken as equal to 10 (Schafer, *et al.*, 1997), in which experience with SCORAD in pre-school children was achieved. So for a risk factor to which 10% of the patients are exposed, and which leads to a 10 point increase in SCORAD, for example 10 to 20 points in SCORAD, 120 patients are needed to give a 90% chance of detecting a difference at the 5% level.

2.5.2 Possible confounding factors

Confounding is a key concept in epidemiology and controlling for it in observational studies is the basis for most designs and statistical methods. A potential confounder must be, by definition, independently related to outcome and the exposure under study (Barker and Rose., 1995). In the design it was possible to control for age where it was restricted to the age group between 5 and 10 years and the multiple regression analyses was used to control for other potential confounders including predictors.

Collection of information about potential confounding factors is a crucial fact that should be taken into account before starting the study. With this information, any statistical analysis can be carried out with and without

adjustment for these potential confounders. The literature provides little information about factors related to the severity of atopic dermatitis and therefore selection of potential confounders cannot be based on hard evidence. However, it was decided in this study that any factor, which has been related to the prevalence of AD could be a potential confounder and controlled for in that particular exposure. Including many confounding factors could confound the results even if they have no real effect what so ever. The following 6 factors were treated as potential confounders and controlled for in all multiple regression analyses (sex, age, area of residency, social class, family size and ethnic background). Other factors treated as potential confounders, when necessary, such as breast-feeding and early onset AD and or any other confounding factor necessitating control in the analysis will be mentioned specifically in that particular exposure.

Nevertheless, no observational design or analytic method can absolutely guarantee that an effect is not confounded to some extent and proof of causality or an effect on the basis of observational research will always have its detractors.

2.5.3 Statistical analysis

2.5.3.1 General

After the study had finished, data were entered in *Epi-Info version 6.04b* statistical software (Dean A, Dean J, Burton, Dicker., 1997) and edited for any human errors. The observer remained blind to results of the questionnaires by not entering the data till the data collection had finished. Therefore the observer was unaware of the exposure under investigation such as age at onset and breast-feeding when the severity assessment was

carried out. This has eliminated any potential measurement bias, except where sex, ethnic group, and area of residence were the exposure. In these factors bias was inevitable and its potential effect on the results will be discussed later in each of these factors. In a simple term, the observer did not know about the risk factors under study apart from those three factors mentioned earlier.

The data then were transferred to *Stata* statistical software *version 6.0* for analysis (Stata Corp. 1999). Descriptive statistics means that results will be presented in the form of tables, figures or percentages, while statistical analysis means presenting results after using statistical tests such as *ordered logistic regression*, or *Wilcoxon test*. Statistical tests were carried out at the 5% level (95% confidence interval and exact p value). Missing data were included in the descriptive statistics when risk of information bias was high, but were otherwise excluded from that particular analysis. Generally “Don’t know” answers were also considered as missing data and excluded from the analysis. *Chi-square (χ^2) test* was used to test for any significant difference between two independent proportions such as sex and visible flexural dermatitis. The *Wilcoxon's Signed Ranks test* was used to detect any significant difference in the scores between two paired observations.

2.5.3.2 Atopic dermatitis severity as the outcome

Eczema severity was measured using the SCORAD Index, which produces a continuous variable. Ranking it into a categorical variable (for example, reducing these to a two-point scale indicating presence or absence) can sacrifice much of the information in the data – information that has been obtained with considerable effort, expense, and patient co-operation. Often, ordered categories are the best available way to capture important

information, such as the stage of disease or the severity of symptoms. Efficient statistical methods for analysing such data have considerable value. The outcome of interest is a continuous variable (the SCORAD scores) skewed to the right, which was expected in a community-based study with mostly mild disease. So non-parametric tests were used for statistical significance, the most powerful of these being *ordered logistic regression* (Anderson., 1984). The "svyolog" command in the *Stata software* (Stata Corp. 1999) estimates an ordered logistic regression for complex survey data and "psu" adjust for repeated measurements on each subject using the actual values at each visit.

It means that, the individual remained the unit of analysis by using the simple mean of the observation. This method uses the response for each individual to form a single mean score that summarises the response curve of that single individual. In simple terms, the individual has remained the unit of the analysis despite using the total number of observations. Summary scores give greater power and less chance of false positive results (Matthews, Altman, Campbell, Royston., 1990).

In this study the outcome of interest was infrequent (severe disease) and the odds ratio with 95% confidence interval and p values will be used to present the magnitude of the difference. It should be emphasised that the study is looking at many factors that may affect disease severity without any prior hypothesis. This may come, however, under the categories of testing multiple hypotheses in which there is a high chance that statistical significance may occur by chance alone and without any real effect. An increase in the number of factors studied in the same study means increasing the chances of getting significant results just by chance (Altman, Gore, Gardner, Pocock., 1995). It

was, therefore, decided prior to starting the study that any results that have a p value of more than 0.05 will be considered as happening by chance and would not be considered as significant findings.

2.5.3.3 Family and children's quality of life as the outcome

When families or children's quality of life was the outcome of interest and atopic dermatitis severity was the exposure under study, *Spearman correlation Coefficient* was used to test for any association between disease severity and QOL at each visit. It was also used to correlate each component of the quality of life questionnaire with disease severity on each visit. *Tobit regression* was used to examine the effect of any potential confounder on the association between QOL and disease severity scores at each visit (Amemiya., 1973; Amemiya., 1984). This assumes that QOL scores has a censored-normal distribution, censored at zero. And values recorded as zero, are regarded as being not exactly known but could be anywhere in the range [minus-infinity to 0]. *Interval regression*, controlling for potential confounders (black skin, child's age, social class, family size, sex, and location) was used to investigate the relationship between changes in severity assessment and quality of life measures (Amemiya., 1973; Amemiya., 1984).

There were 34 body areas examined and recorded on the examination sheet (Table 3). To make a relevant clinically meaningful comparison, the 34 areas were grouped into 5 major areas (Face and neck, chest and abdomen, upper limb, back, and lower limb). In this way, it was possible to make a sensible comparison of the QOL scores between areas with visible eczema and those free of eczema and between each other.

3 CHAPTER 3 RESULTS

3.1 Section 1: General results

3.1.1 Recruitment and response rate

General practitioners (GPs) from 9 practices in south London and mid Wales provided names and addresses of 377 subjects, who were contacted by post. The response rate in the urban area (35%) was significantly lower than in the rural area (78%), Table 4. Information about the non-responders is not available. These are subjects who failed to respond after contacting them up to three times and it was not feasible to gather any further information from these subjects.

Table 4. Number contacted, response rate and number included in the study

Area of residence	Practice number	Number contacted	Number (RR%)	Number included in the study from those who responded (%)
U R B A N	One	150	52 (35)	45 (87)
	Two	19	5 (26)	4 (80)
	Three	27	8 (30)	2 (25)
	Four	36	13 (36)	11 (85)
	Five	38	12 (32)	9 (75)
	Six	33	17 (52)	11 (65)
	Total	303	107 (35)	82 (77)
R U R A L				
	Seven	21	21 (100)	21 (100)
	Eight	29	23 (79)	21 (91)
	Nine	24	14 (58)	13 (93)
	Total	74	58 (78)	55 (95)
Nine practices		377	165 (44)	137 (83)

RR; Response Rate

3.1.2 Clinical examination

Of 165 subjects who responded, 21 children were excluded from the study before clinical examination. Of these 21, 7/165 (4%) did not turn up for three

different appointments, 4/165 (3%) had moved out of the area, and 10/165 (6%) were excluded before examination because they had never had eczema (they answered “No” to the last question in the UK diagnostic criteria one-page-postal questionnaire (see question number 6 in Appendix 6.1).

Of 144 children who were clinically examined, 137 were eligible to be included in the study. The reasons for excluding 7/144 (5%) children, with their UK diagnostic criteria characteristics, are summarised in Table 5.

Table 5. Reasons for excluding 7 children after clinical examination

No.	Practice number	Reasons	UK diagnostic criteria	
			Major	Minor
1	One	Had a rash only once	0	2
2	One	Vitiligo around the mouth	1	1
3	Two	Anaemia and pruritus	1	1
4*	Three	Angular stomatitis only	1	4
5*	Three	Has AD but her father was interested in receiving treatment and not just observation	1	3
6	Three	Lichen Nitidus	0	1
7	Nine	Young age (Date of Birth 1994)	.	.

*Has fulfilled the UK diagnostic criteria

3.1.3 Inclusion criteria

The UK diagnostic criteria for AD were used to define cases of atopic dermatitis. These contain one major criterion and 5 minor criteria (Williams, *et al.*, 1994a; 1994b; and 1994c). A subject must have one major criterion and three minor criteria to fulfil the criteria and qualify as a case of AD. Description of each criterion for this population is as follows:

3.1.3.1 Itchy skin condition in the last 12 months

Itching in the last 12 months is the only major criterion in the UK diagnostic criteria for atopic dermatitis (Williams, *et al*, 1994a). One hundred and thirty-five (98.5%) children had an itchy skin condition in the last 12 months, and 2 (1.5%) children were not itchy in the last 12 months.

3.1.3.2 Onset below the age of two

Eczema starting before 2 years of age is one of the 5 minor criteria in the UK diagnostic criteria for AD. One hundred and eleven (82%) patients had eczema before the age of 2 and the rest (18%) their eczema started when they were older than 2 years. The late onset population included 14 children whose eczema started between the age of 3 to 4, and 10 children whose eczema started between the age of 5 to 10.

3.1.3.3 Skin crease involvement

In 119 (87%) children, the eczema had affected the skin creases in the past, 14 (10%) never had affected the skin creases and data were missing in 4 children (3%).

3.1.3.4 Personal history of other atopic disease

The answer was yes to the question “has your child ever suffered from any atopic disease (asthma and/or hay fever)” in 87 (64%) children, and no in 50 (36%) children. There was a positive history of asthma in 59 (43%) and hay fever in 62 (45%) children before joining the study.

3.1.3.5 History of generally dry skin in the last 12 months

One hundred and seventeen patients (87%) had suffered from generally dry skin in the last 12 months. Three missing values were not included in this percentage.

3.1.3.6 Visible flexural dermatitis

Flexural dermatitis is the only sign in the UK diagnostic criteria. It was seen in 74 (54%) children on the day of clinical examination. The analysis revealed no significant difference in frequency of flexural dermatitis between 39 (53%) girls and 35 (47%) boys ($p = 0.97$, χ^2 test).

3.1.3.7 Fulfilling the UK diagnostic criteria for atopic dermatitis

After clinical examination and assessment of flexural dermatitis, 123 (90%) children fulfilled the UK diagnostic criteria (Williams, *et al.*, 1994a; 1994b; and 1994c). Of 123 children who satisfied the criteria, 34 (25%), 42(31%) and 47(34%) had five, four and three minor criteria respectively. Fourteen (10%) children did not fulfil the criteria; 11 (8%) of these had one major and two minor criteria. Three (2%) children had the following: the first had no major and one minor; the second, one major and no minor; and the third, had a positive history of eczema but did not have any of the criteria. Table 6 shows the descriptions of the 14 subjects who did not fulfil the criteria.

Table 6. Description of children who did not fulfil the UK diagnostic criteria for atopic dermatitis, but they had or had had the disease

Description of 11 (8%) children who had one major and two minors criteria	Description of three (2%) children who did not fulfil the criteria
1. Eczema has cleared now. The minors were hay fever and early onset. 2. Late onset eczema 5-10 years. The minors were skin creases and dry skin. On examination there is hyperpigmentation below the buttocks, which might indicate active eczema before. 3. Late onset eczema and has cleared now. Minors were hay fever and dry skin. 4. Age of onset was 3-4 years. Minors were hay fever and dry skin. 5. Late onset 5-10 years. The minors were dry skin and flexural dermatitis. 6. Age of onset was 3-4 years. The minors are asthma and dry skin. 7. Onset at 3-4 years. The minors were dry skin and flexural dermatitis. 8. Eczema has cleared. The minors are onset under 2 years and dry skin. 9. Eczema cleared now, but it never affected the skin creases (extensor eczema). The minors are onset under 2 years and dry skin. 10. Eczema has cleared now. The minors are skin creases and dry skin. On follow-up excoriation was seen on the back of his forearms. He has MC*. 11. Eczema has cleared. The minors are onset under 2 years and dry skin	1. One major and the one minor was dry skin. Age of onset was 5 to 10 years. 2. No major and the two minors were dry skin and flexural dermatitis. He has MC*. 3. No major neither any of the minors, but positive history of eczema that probably has cleared now. Data about age of onset and skin creases involvement were missing.

*MC; Molluscum Contagiosum

A decision had to be made as to whether to include these 14 children or exclude them from the analysis. However, prior to making such decision sensitivity tests were carried out before and after excluding this group of patients (14 children) to investigate any significant difference in the outcome between these two groups.

For instance, when the urban area was compared with the rural area, the risk of severe disease was 1.87 higher in the urban area than rural area when the 14 patients were included. However, the risk remained significant and almost the same (1.93 higher) even after excluding these 14 children (see Table 7).

Table 7. Odds ratio for severe disease in children who live in the urban area by those who fulfilled the criteria, who did not and the total sample included

Subjects included in the analysis (Number of children)	OR	95%CI	P value
Total sample (137)	1.87	1.12 to 3.11	0.017
Fulfilled the criteria (123)	1.93	1.13 to 3.3	0.016
Did not fulfil the criteria (14)	2.95	0.56 to 15.56	0.18

OR; Odds Ratio. CI; Confidence Interval

Table 7 showed that the risk of severe disease in those who lived in an urban area and did not fulfil the criteria (14 children) was still higher, but statistically insignificant. Although the risk was statistically insignificant, the odds ratio value still lies within the 95% confidence interval of those who fulfil the criteria. This could represent a type II error by accepting that there were no differences, when in fact there were true differences. A type II error could have happened because of the small number of subjects reflected by a very wide confidence interval.

The results shown in Table 7 suggest that there were no systematic differences between these two populations (who fulfilled or did not fulfil the

UK diagnostic criteria for AD), and therefore the sample should include both as they represent subjects with similar behaviour.

Another example was the relationship between disease severity and the children's quality of life. There was no significant difference in the outcome before and after excluding those children who did not fulfil the criteria as shown in Table 8. It was almost the same.

Table 8. Correlation between CDLQI and SCORAD before and after excluding those children who did not fulfil the UK diagnostic criteria for AD

QOL Visit 1 (March 99)		QOL Visit 2 (October 99)	
Total sample	After exclusion	Total sample	After exclusion
$r = 0.42$ ($p < 0.001$)	$r = 0.44$ ($p < 0.001$)	$r = 0.46$ ($p < 0.001$)	$r = 0.47$ ($p < 0.001$)

r, correlation coefficient. QOL; Quality of life. P; p-value

When the relationships between changes in DFI and the SCORAD-D were investigated using multiple regression analysis, each unit change in SCORAD-D was associated with a 0.17 (95%CI, 0.06 to 0.29, $p = 0.002$) units change in family quality of life. The outcome has remained the same and was also statistically significant (Regression Coefficient (R) = 0.16, 95%CI, 0.05 to 0.28, $p = 0.004$) after excluding cases that did not fulfil the criteria.

It was clear that there were no substantial differences before and after excluding the 14 children who did not fulfil the UK diagnostic criteria for AD. Based on the previous finding, the high percentage (90%) of those fulfilled the criteria and the prospective design of the study, it was decided to include these children in the study and carry out all the analyses with these subjects being included.

3.1.4 Subjects Included

The number recruited during the three visits was 137 children, 82 (60%) and 55 (40%) children from the rural and urban areas respectively. The gender ratio was almost balanced in the total population (see Table 9). The age range was 5 to 12 years and the mean age was 8 (SD: 1.6) years. The 137 children included in the study were primarily interviewed and examined during the following dates; 40 (29%) in March 1998, 70 (51%) in October 1998, and 27 (20%) in March 1999. Details of recruitment and follow-up are shown in Table 10. No more new subjects were recruited after the third visit.

Table 9. Sex distribution of newly recruited children by each visit

Time	Number of children newly recruited at each visit (%)	Male (%)	Female (%)
March 98	40 (29)	17 (43)	23 (57)
October 98	70 (51)	38 (54)	32 (46)
March 99	27 (20)	10 (37)	17 (63)
Total	137	65 (48)	72 (52)

Table 10. Number of patients on recruitment and follow up

Frequency*	March 98	October 98	March 99	October 99
Four times	40	34/40 (85%)	33/40 (83%)	35/40 (88%)
Three times	-----	70	56/70 (80%)	65/70 (93%)
Two times	-----	-----	27	20/27 (74%)
Total seen per visit	40	104	116	120/137 (88%)

Shaded number represent newly recruited patients at that time
*Frequency of severity assessment per each group of patients

In all, 29 (21%) children attended the four visits, 84 (61%) attended the last three visits and 106 (77%) were seen in both March 1999 and October 1999 (see Table 10). By the end of the study, 17 (12%) children did not turn up for their last appointments and this led to an 88% follow-up rate. With this high

follow up rate any potential substantial difference between these two groups would be less likely to have any significant effect on the outcome.

3.1.5 Course of AD

3.1.5.1 Severity of eczema when first started and at each visit

Parents were asked retrospectively to grade their children's eczema at onset on a 0 to 10 scale. Parents of 132 (96%) children rated their children's eczema and data were missing for 5 children. The mean severity score at onset was 5.02 (SD 2.8, range 0 to 10) and median 5 (95%CI, 4 to 5). At each visit parents were asked to rate the child's eczema on the same scale. The mean score at the final visit was 2.1 (SD 2.2) and median 1 (95%CI, 1 to 2) representing highly significant improvement in disease severity as rated by the parents ($p < 0.001$). It appears that parents had seen a significant improvement in their children's eczema severity between the time when the eczema first started and the date of the final visit.

3.1.5.2 Best season in the year for eczema

Parents of 28 (20%), 12 (9%), 52 (38%), and 4 (3%) children felt that their children's eczema was at its best condition during winter, spring, summer, and autumn respectively. In 41 (30%) children there was no difference between the four seasons. In general, summer was the best season for eczema while 30% showed no seasonal variation.

3.1.5.3 Apply or ever applied steroid cream/ointment

Parents of 123 (90%) children applied or had ever applied steroid cream/ointment to their children's skin before joining the study; 11 (8%) children had never applied topical steroids, with no data for 3 (2%) children. There was no significant difference between males and females in steroid

usage ($p = 0.9$, χ^2). However the mean SCORAD was higher in those who used topical steroids 11.2 (SD 11.5) than those who did not apply topical steroids 5.8 (SD 5.8). Although the difference was statistically significant (OR = 1.86, 95%CI, 1.03 to 3.36, $p = 0.038$), it does not have any significant clinical implication because topical steroid was more likely to be used in children with severe disease, but this statistically significant finding validates the usage of the SCORAD index in severity assessment. It suggests that the system was able to give high scores for those with more severe disease.

3.1.5.4 Frequency of topical steroid application

Parents were asked about the frequency of topical steroid application in the time preceding each visit. The figures from the fourth visit were more consistent as this represents the frequency of topical steroid usage in the last 6 months only, yet figures from first, second and third visits represent a mixture of 6 and 12 months recall times; question number 34 in the recruitment questionnaire (Appendix 6.2) and question number 20 in the follow-up questionnaire (Appendix 6.3).

Answers from the fourth visit (October 1999) have the same recall time, and therefore, these were reported. Parents of 10 (9%), 5 (4%), 11 (9%), and 48 (41%) children had applied topical steroids twice a day, once a day, every other day, and less frequently respectively. However, parents of 43 (37%) children had never applied topical steroids to their children's skin before the fourth visit. Parents of three children did not answer this question. These figures are consistent with the fact that most cases were in mild form and did not necessitate topical steroids. Nevertheless, "steroid phobia" cannot be excluded from the data available.

As answers from the fourth visit were more consistent (all parents answered the same question with 6 months recall time), they were used to investigate if there was a trend in the objective severity scores with increased topical steroid frequency.

The mean observer’s score (SCORAD-D) was higher at any frequency of topical steroid application (9.3) than the no category (4.7). The observer was able to give higher scores for those who applied steroids than those who never used topical steroids in the last 6 months. A small number of observations indicating once a day application (5 children, 4%) might explain the low main score in that category. The low number of children in a once a day category may have affected the trend in the parent’s grading of the child’s eczema, see Table 11.

It is also quite clear from Table 11 that the parents were able to give higher scores when the application of topical steroids became more frequent. This suggests that the questionnaire used in this study has an internal consistency.

Table 11. Mean (SD) and median (95%CI) of the SCORAD-D and the mean (SD) parents grading of child’s eczema at the fourth visit for each frequency of topical steroid applied before this visit

Frequency of application	SCORAD-D		Mean scores of the parents’ grading of the child’s eczema (SD)
	Mean (SD)	Median (95%CI)	
None	4.7 (7.2)	0 (0 to 7)	1.7 (1.4)
Less frequently	9.04 (9.2)	8 (0 to 12)	2.1 (2.0)
Every other day	12.4 (8.8)	11 (5.7 to 19.7)	3.1 (2.7)
Once a day	5.2 (7.3)	0 (0 to 15)	1.8 (2.5)
Twice a day	12.2 (13.6)	9 (0 to 29.9)	4.2 (3.1)
Missing values	0	0	§

§ In this category, data were missing for two children and parents scored 8 for the third child.

3.1.5.5 Admission to hospital

Before the first visit only one patient was admitted to the hospital because of eczema. Before the third visit two patients were admitted to the hospital because of their eczema. No one was admitted to the hospital before the second and fourth visits.

3.1.5.6 Systemic treatment

Again the recall time was different at the first three visits regarding the usage of systemic remedies. Therefore, information from the final visit was more consistent as parents completed the same question with a 6 months recall time. Before the final visit, 20 (17%) children had taken systemic antibiotics for their eczema, 22 (19%) children had taken oral antihistamines because of their eczema, while systemic steroids were used in 2 (1.7%) children for their eczema. In this study no child had used systemic cyclosporin or azathioprine at any time.

The mean scores of the SCORAD-D at the fourth visit were looked at to assess the internal consistency and validity of the question. It was clear that children who received antibiotics and/or prednisolone had higher mean scores than those who did not. However, there was no difference in the mean score between those who were receiving oral antihistamines and those who did not (see Table 12). But the subjective symptom scores were higher 3.6 (SD 3.2) for those receiving oral antihistamines than those who did not 2.8 (SD 3.4).

Table 12. Mean SCORAD-D per each systemic treatment taken in the last 6 months preceding the final visit

Systemic treatment	Mean SCORAD-D (SD)	
	Yes	No
Antihistamine	7.9 (9.0)	7.9 (9.1)
Antibiotic	9.4 (10.0)	7.6 (8.9)
Prednisolone	26.5 (10.6)	7.5 (8.8)

3.2 Section 2: Atopic Dermatitis Severity

3.2.1 Description of the atopic dermatitis severity

3.2.1.1 Total number of observations

The total number included 137 subjects, each seen on up to 4 occasions, which represented 380 observations (69% out of an expected 548). There was no data for 168 (31%) observations, and of these, 124 (23%) observations were “missing” due to the fact that the required number were not interviewed during the first and second visits. The remaining 44 (8%) observations were unavailable because subjects had not attended the follow up appointments on visits 2, 3 or 4. The SCORAD Index was used to assess atopic dermatitis severity and as mentioned earlier, it has two components (signs and symptom evaluation).

3.2.1.2 The total SCORAD

When the total SCORAD from the four visits was considered, the minimum and maximum scores were 0 and 66 respectively and the mean and median of the total SCORAD with numbers of patients per each visit are shown in Table 13. The mean SCORAD improved at the second (October 98) and fourth (October 99) visits, which took place in autumn, one year apart and deteriorated in March 1998 and 1999.

Table 13. Mean (SD) and median (95%CI) of the SCORAD with number of subjects per visit

Visit	Number*	Mean SCORAD (SD)	Median (95CI%)
One (Mar. 98)	40	9.8 (8.4)	7.5 (5.3 to 12.7)
Two (Oct. 98)	104	9.4 (10.4)	7.5 (6 to 8)
Three (Mar. 99)	116	12.1 (12.6)	9 (7 to 11)
Four (Oct. 99)	120	10.7 (11.4)	7 (4 to 11)

SD: Standard deviation. *: Total number of subjects seen per visit. CI: Confidence Interval

Figures presented in Table 13 may have been contaminated by the subjects newly recruited at the first three visits. Looking at each individual group of patients separately was important in order to evaluate if these subjects had similar patterns compared with the total number shown in Table 13 or the inclusion of new subjects had deviated the scores at each visit. It also will show the changes of severity for each of these subgroups.

Figure 6 shows that the 29 children attending all the four visits, 55 attending the last three visits but not the first, and 20 children attending the last two visits only had a similar SCORAD pattern compared with the mean SCORAD for the total number at each visit. The mean SCORAD, for the total number attending each visit, shown in Figure 6, is a duplicate of the mean SCORAD shown in Table 13. The repetition was used for comparison between the total number and the three subgroups. It is therefore quite clear that the inclusion of new subjects at visits two and three did not contaminate the data and the pattern of AD severity got worse in March and improved in October but remained the same for each of these subgroups as well as for the total sample.

Figure 6 shows also disease fluctuation over time, a finding that was to be expected in a chronic relapsing disease such as AD (Rajka., 1989a). Preliminary analysis of the data could not explain the changes between visits on the basis of the information available from questionnaire about the potential risk factors. However, the changes in disease severity might be explained by the seasonal variation as the second visit came after winter (majority got worse) and the third visit came after summer (majority got better).

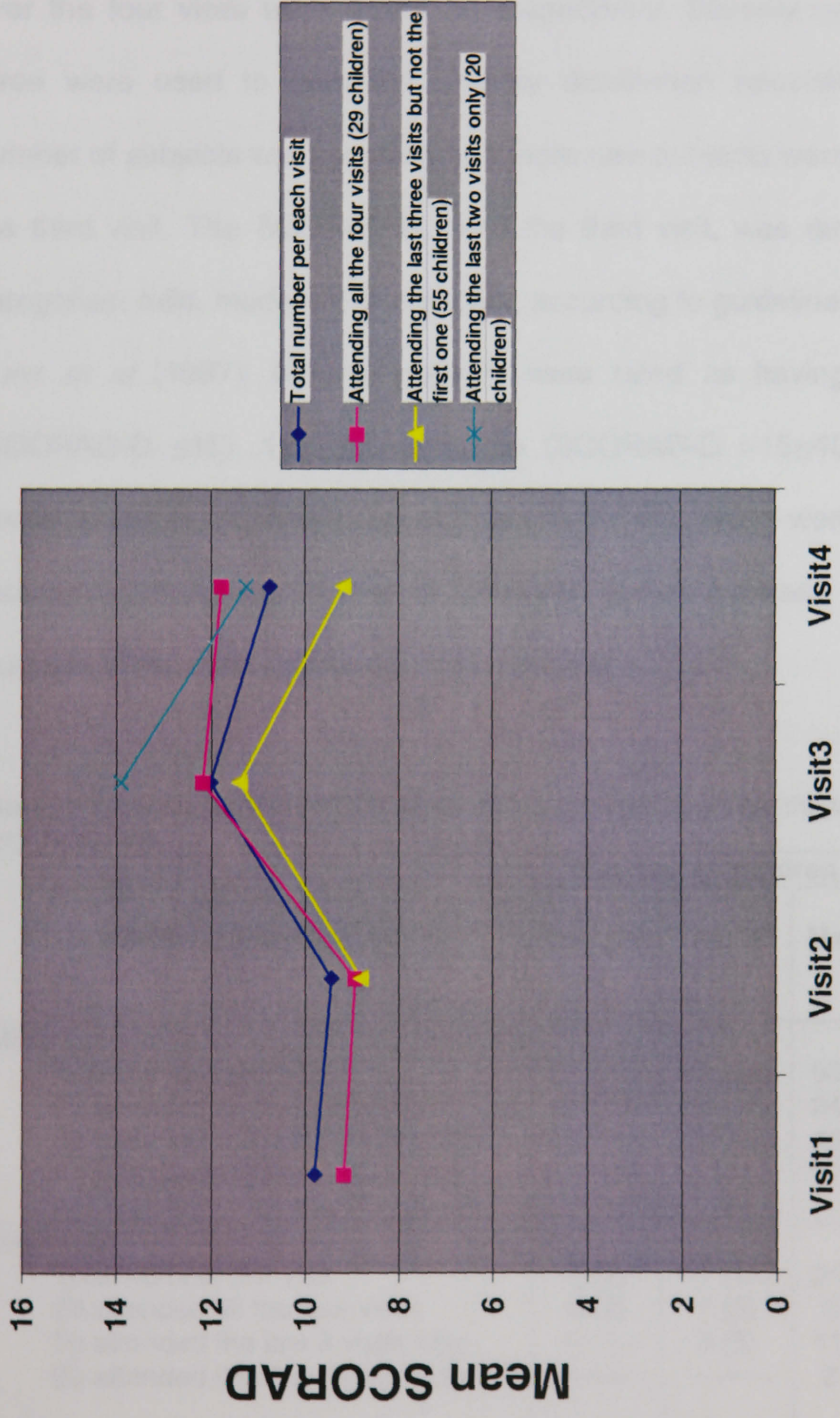


Figure 6. Mean SCORAD per each visit for the total sample and each subgroup

3.2.1.3 Objective score

The objective SCORAD (SCORAD-D) included only the intensity and extent components of the SCORAD index. The highest and lowest observer scores over the four visits were 0 and 56 respectively. Severity scores from visit three were used to rank the severity distribution because the required number of subjects was recruited and more new subjects were recruited after the third visit. The SCORAD-D, from the third visit, was ranked into three categories; mild, moderate and severe, according to guidelines suggested by Kunz *et al* (1997), 80% of patients were rated as having mild eczema (SCORAD-D ≤ 15), 18% as moderate (SCORAD-D $>15 \leq 40$), and 2% as severe eczema (SCORAD-D > 40) (see Table 14). There were no significant statistical differences in the SCORAD-D scores between the visits, for example in the third and fourth visits $p = 0.74$.

Table 14. Severity (Ranked SCORAD-D) distribution per visits for the total number and each subgroup

Severity Distribution	Number of children per visit (%)			
	Mar. 98	Oct. 98	Mar. 99	Oct. 99
Mild				
Total number per visit	37 (93)	92 (88)	93 (80)	98 (82)
29 attended all the four visits	27 (93)	28 (97)	24 (83)	23 (79)
55 attended the last 3 visits only	-----	49 (89)	43 (78)	47 (85)
20 attended the last 2 visits only	-----	-----	17 (85)	17 (85)
Moderate				
Total number per visit	3 (7)	11 (11)	21 (18)	22 (18)
29 attended all the four visits	2 (7)	1 (3)	5 (17)	6 (21)
55 attended the last 3 visits only	-----	5 (9)	11 (20)	8 (15)
20 attended the last 2 visits only	-----	-----	2 (10)	3 (15)
Severe				
Total number per visit	0 (0)	1 (1)	2 (2)	0 (0)
29 attended all the four visits	0 (0)	0 (0)	0 (0)	0 (0)
55 attended the last 3 visits only	-----	1 (2)	1 (2)	0 (0)
20 attended the last 2 visits only	-----	-----	1 (5)	0 (0)

It can be concluded from Table 14 that the vast majority of children have atopic dermatitis in its mild form. The table also shows that inclusion of new subjects did not deviate the severity distribution with the majority being mild for any subgroup.

Another way of looking at this group of patients, to avoid the effect that might be introduced by new subjects each time, is to rank the disease severity for the 137 children included in this study. These are subjects recruited on three occasions over one year. The severity distribution was similar to those who attended the third visit (mild 87%, moderate 11%, and severe 2%).

3.2.1.4 Subjective symptoms scores

Observer's scores were excluded and parents' scores only were used to look at the trend of parents' assessment of itching and sleep loss (subjective symptoms). Parents' score of subjective symptoms produces the same trend as for the observer scores (see Table 15), except for the 29 children who attended all the four visits. They tend to have higher mean scores and do not follow a similar trend. This can be explained by the origin of these subjects as all of them were from the urban area.

Table 15. Number of children and the mean (SD) subjective symptoms scores per each visit for the total sample and each subgroup

Number of children seen	Mean (SD)* per visit			
	Mar. 98	Oct. 98	Mar. 99	Oct. 99
Total number included	3.7 (4.0)	3.1 (3.9)	3.7 (3.8)	3.0 (3.6)
29 attended all the four visits	3.4 (4.0)	4.6 (4.4)	4.7 (4.5)	3.5 (3.9)
55 attended the last 3 visits only	-----	2.2 (3.2)	3.0 (3.1)	2.1 (2.5)
20 attended the last 2 visits only	-----	-----	4.7 (4.2)	3.5 (3.9)

Mean (SD) of Subjective symptoms scores

However, there was statistically significant improvement in the subjective symptom scores between the third and fourth visits ($p = 0.008$). The summer holiday preceding the fourth visit could be the real factor that had led to improvement, or there might be a subtle clinical improvement that the observer was unable to detect it. But generally the scores showed significant correlation with the observer's scores, which reflects the internal consistency of the SCORAD (see Table 16).

Table 16. Correlation between the SCORAD-D (Observer scores) and the subjective symptoms scores (parents score) in each visit

Visit One	Visit Two	Visit three	Visit four
$r = 0.29$ ($p = 0.07$)	$r = 0.45$ ($p < 0.001$)	$r = 0.56$ ($p < 0.001$)	$r = 0.53$ ($p < 0.001$)

r, Correlation coefficient. *P*; p-value

3.2.1.5 Parents grading of disease severity

In the recruitment and follow-up questionnaires parents were given the opportunity to grade their child's eczema on a 0 to 10 scale at that time (0 no eczema and 10 the worst eczema the child ever had). Number and the mean scores of parental grading are shown in Table 17.

Table 17. Number of children and the mean (SD) score of parental grading of the child’s eczema per each visit for total number and subgroups

Number of children seen	Mean (SD)* per visit			
	Mar. 98	Oct. 98	Mar. 99	Oct. 99
Total number included	2.3 (2.1)	2.0 (2.0)	2.5 (2.3)	2.1 (2.2)
26 attended all the four visits (no data for 3 children)	2.0 (1.6)	2.8 (1.9)	3.2 (2.8)	2.6 (2.6)
53 attended the last 3 visits only (no data for 2 children)	-----	1.3 (1.7)	2.2 (2.2)	1.7 (1.8)
18 attended the last 2 visits only (no data for 2 children)	-----	-----	2.8 (2.2)	2.4 (2.3)

*Mean (SD) of severity grading by the parents

Parents’ grading of disease severity was significantly correlated to the investigator assessment (SCORAD-D) of disease severity using the SCORAD index (sign scores only). Table 18 shows this is a highly significant and consistent correlation during the four visits.

Table 18. Correlation between the SCORAD-D (Observer scores) and the parents assessment of disease severity (in the questionnaire) at each visit

Visit One	Visit Two	Visit three	Visit four
$r = 0.50$ ($p = 0.001$)	$r = 0.41$ ($p < 0.001$)	$r = 0.57$ ($p < 0.001$)	$r = 0.56$ ($p < 0.001$)

r, Correlation coefficient. *P*; p-value

3.2.1.6 Summary of severity description

- The total SCORAD, SCORAD-D, subjective symptom scores, and global assessment have the same trend, except at visit one.
- In most cases (80%) the eczema was in its mild form, a finding that had been expected in community-based study.
- The total SCORAD, sign scores and global assessment showed insignificant fluctuation in disease severity between the visits. This was expected in an observational study without any active interventions. There was however a significant improvement in the subjective symptom scores between the third and fourth visits.

3.2.2 Atopic dermatitis severity over time as the outcome

This is a longitudinal study and the outcome was disease severity over time. The total number of observations over the four visits was used in the statistical analysis controlling for each repeated measure as mentioned earlier. In other words, the subject remained the unit of analysis, despite using the total number of observations (Matthews, Altman, Campbell, Royston., 1990).

Figure 6 shows that there are three subgroups of subjects with similar severity changes over time. However, sub-analysis of each group should be carried out to evaluate if these subjects have a similar increased risk of severe disease over time or whether a substantial difference did exist.

The first was accomplished by looking at the description of these groups. Table 19 shows that the mean scores of SCORAD for those who attended one follow-up visit and who attended more than one follow-up are almost the same. The lower severity scores in the two follow-up subgroups could be explained by the high percentage of new subjects recruited from the rural area (80%), who always showed low scores, and high severity scores in the one follow-up subgroup could be explained by the high percentage of subjects from the urban area (90%). Table 19 also shows that there were no substantial differences in the demographic characteristic of these groups, except for those who attended three follow-ups where there was more unemployment. These subjects were recruited from one practice in an urban area, where there is large number of council houses.

Table 19. Follow-up characteristic of the study population per number of follow visits for each subgroup

Variables name	Number of follow-up visits		
	One (n = 20)	Two (n = 55)	Three (n = 29)
Age in years (mean)	8.0	7.1	7.5
Sex, %Male	40	58	41
SCORAD, mean (SD)	13.9 (15.4)	8.8 (10.0)	9.2 (7.8)
SCORAD-D, mean (SD)	9.3 (12.7)	6.6 (7.8)	5.8 (5.8)
Subjective Symptoms, mean (SD)	4.7 (4.2)	2.2 (3.2)	3.8 (4.1)
Ethnic group			
White	13 (65%)	51 (93%)	15 (52%)
Black skin	4 (20%)	3 (5%)	9 (31%)
Other races	3 (15%)	1 (2%)	5 (17%)
Social class			
One	5 (15%)	8 (15%)	3 (10%)
Two	5 (25%)	15 (27%)	5 (17%)
Three non-manual	3 (15%)	12 (22%)	8 (28%)
Three manual	0	2 (4%)	0
Four	3 (15%)	9 (16%)	3 (10%)
Five	1 (5%)	6 (11%)	0
Unemployed	5 (25%)	3 (5%)	10 (35%)
Area of residence			
Urban	18 (90%)	11 (10%)	29 (100%)
Rural	2 (10%)	44 (80%)	0

n; number of children seen

Secondly, data analysis was carried out using Stata’s -svy- commands for repeated measures (in particular –svyolog-), the primary sampling unit being the subject. All values are used to produce appropriate estimates and the standard errors then adjusted using the Huber sandwich estimator. This approach ensures that all information is fully used, but that the standard errors are appropriate. The net effect is a modest, but entirely appropriate increase in power and decrease in standard error. To confirm the robustness of the findings, the analysis was repeated in a number of ways for the one most important risk factor (onset during first year of life):

1. For 3 subgroups: those with complete data from 2 visits, 3 visits and all 4 visits, results were similar for the 3 subgroups. The 3 subgroups have similar tendency of increased risk for severe disease with an odds ratio around 2 lying within the 95% confidence interval of the

total group without reaching the statistical significance in the 2 visits subgroup. Although not significant, it was not possible to say that there was no association because this may present a type II error. Type II error could have happened due to the small number of subjects included in the sub-analysis which was reflected by relatively wider 95% confidence interval, see Table 20. Urban area as an exposure has a similar outcome when the sub-analysis was carried out, see Table 21. It should be explained here that the 29 children attending all the four visits were not included in this analysis because they were all recruited from the urban area, and not because they different in other ways from the other two groups.

2. With adjustments for a main effect of visit, there was no significant main effect of time ($F_{3, 135} = 0.92, p=0.43$).
3. With a visit onset interaction term, there was no significant main effect of time by onset interaction ($F_{3, 135} = 0.45, p=0.72$).

However, the analysis is mentioned for other risk factors only where there is evidence of a complication.

Table 20. Risk for severe disease (exposure onset during the first year) per each group of patients

Number of children seen	OR	95%CI	P value
Total number included	2.1	1.2 to 3.3	0.006
29 children who attended all the four visits	2.56	1.03 to 6.33	0.043
55 children who attended the last 3 visits only	2.67	0.99 to 7.09	0.05
20 children who attended the last 2 visits only	1.3	0.34 to 5.2	0.67

OR; Odds Ratio. CI; Confidence Interval

Table 21. Risk for severe disease (exposure urban area) per each group of patients

Number of children seen	OR	95%CI	P value
Total number included	1.87	1.12 to 3.11	0.017
55 children attended the last 3 visits only	3.5	0.9 to 13.4	0.06
20 children attended the last 2 visits only	1.2	0.3 to 4.3	0.79

OR; Odds Ratio. CI; Confidence Interval

It can be concluded from the results shown in Tables 19, 20, and 21 and the sub-analysis that these three subgroups and the total number included follow similar disease patterns over time. Therefore, the total number of observation per visit is a valid grouping and will be included in the longitudinal analysis controlling for each observation. In other words, the subject remained the unit of analysis and was not a duplicate number of observations.

3.2.2.1 Intrinsic factors as the exposure

3.2.2.1.1 Age at onset

Parents of 93 (68%) children reported onset of eczema during the first year of life, 21 (15%) at the age of 2, 18 (13%) at 2-6 years and 4 (3%) at 7 years or more. Table 22 shows the distribution by area of residency. There was not any marked sex difference in children whose eczema started during the first year of life, 49 (53%) females and 44 males, $p = 0.93$ (χ^2).

Table 22. Distribution of age at onset of eczema of the whole, urban and rural population

Age of onset	Whole population (%)	Urban (%)	Rural (%)
6 months or less	64 (47)	40 (49)	24 (44)
7-12 months	29 (21)	19 (23)	10 (18)
13-24 months	21 (15)	10 (12)	11 (20)
2-6 years	18 (13)	9 (11)	9 (16)
7 years or more	4 (3)	3 (4)	1 (2)
Missing	1 (1)	1 (1)	Nil (0)
Total	137	82	55

The odds of having severe disease was almost two times more in children with eczema that started during the first year of life (OR = 2.1; 95% CI, 1.2 to 3.3, p = 0.006). Onset during the first year remained as an independent predictor for disease severity after adjusting for potential confounders, which included breast-feeding for any duration (OR = 2.1; 95%CI, 1.2 to 3.5, p = 0.008). This remained significant even after exclusion of the parents' score from the SCORAD, (OR = 1.9; 95%CI, 1.15 to 3.22, p= 0.013). Therefore, children with eczema starting during the first year of life are almost two times more likely to have severe disease than those with eczema that started later.

3.2.2.1.2 Ethnic group

The ethnic group of the child was defined according to the parents' response to question number 5 in the recruitment questionnaire (see Appendix 6.2). One hundred and thirty-three children were born in the UK, and of the remaining 4 children; one was born in the USA, one in Canada, one in West Germany, and the country of birth was missing in one child. The parents of the last child considered him to be in the “other” ethnic group. All these 4 children had been living in the UK for 5 years or more.

The urban population contained 42 (51%) Caucasians. This is because the population of the area studied contained a high proportion of patients from

minority groups e.g. 26 (32%) black. All black children were borne in the UK. The rural population were 100% Caucasian (Table 23).

Table 23. Ethnic background distribution of the whole, urban and rural populations

Ethnic group	Whole sample (%)	Urban (%)	Rural (%)
White	97 (70.8)	42 (51)	55 (100)
Black African	11 (8)	11 (13)	None
Black Caribbean	13 (9.5)	13 (16)	None
Black Other	2 (1.5)	2 (3)	None
Indian	1 (0.7)	1 (1)	None
Bangladeshi	1 (0.7)	1 (1)	None
Other group	10 (7.3)	10 (12)	None
Not applicable	2 (1.5)	2 (3)	None
Total	137	82	55

3.2.2.1.2.1 Black Skin

In the total population parents of 26 (19%) children considered their children of black origin. On a crude analysis, children with black skin are at a non-significant risk of severe disease (OR = 1.06; 95%CI, 0.56 to 2.00 p = 0.84). This risk became highly significant after adjusting for erythema score (OR = 7.52; 95%CI, 2.56 to 22.62, p < 0.001) with relatively wide confidence interval. Erythema can be very difficult, if nearly impossible, to see on black skin. Erythema scores also form nearly 10% of the total SCORAD and 12.5% of SCORAD-D. It is therefore independently associated with the exposure (black skin) and the outcome (atopic dermatitis severity), thus erythema score is a true confounder.

This relationships stayed highly significant when subjects with erythema score equal to zero were only included (OR = 6.21; 95%CI, 2.76 to 13.96, p < 0.001). The risk remained high and statistically significant even after controlling for other potential confounders (social class, area of residence,

sex, child's age, and family size) (OR = 5.56; 95%CI. 1.91 to 16.18, p = 0.002).

To determine whether other source of bias had perhaps affected the outcome other than erythema scores, the SCORAD index was excluded and parents' grading of disease severity on a 0 to 10 scale was used as the outcome of interest. It was found to be completely independent of the SCORAD index and the investigator had no influence on it but it was significantly correlated to his scores (Table 18). Children with black skin were at a significant higher risk of having severe disease than their white counterparts (OR = 3.66; 95%CI, 2.04 to 6.55, p < 0.001). This risk remained highly significant after controlling for area of residence, social class, family size, sex, and child's age (OR = 2.55; 95%CI, 1.28 to 5.11, p = 0.008). Exclusion of children from the rural area had no effect on the outcome (OR = 2.39; 95%CI, 1.24 to 4.61, p = 0.01).

In summary, children with black skin who have AD are about six times more likely to have severe disease than their white counterparts. This risk remained highly significant when parents assessed disease severity and after adjusting for potential confounders. Reliance on erythema scores in severity assessment system can mask severe disease in black children.

3.2.2.1.2.2 Other Ethnic groups

As shown in Table 23, the number of children with AD from "other" ethnic groups was very small. Also they have differing genetic backgrounds, thus, they were not considered for further analysis.

3.2.2.1.3 Child's atopy (asthma/hay fever)

The data described here was collected from the one-page questionnaire of the UK diagnostic criteria for AD. Sixty-two (45%) and 59 (43%) children had a positive history of hay fever and asthma respectively. In total, 87 (64%) children had a history of atopy before joining the study.

3.2.2.1.3.1 Child's hay fever

Children who had ever had hay fever were 2.5 times more likely to have severe AD than those who did not (95%CI, 1.44 to 4.3, $p = 0.001$). Bronchial asthma in a child could be a potential confounder. Nevertheless, children with hay fever are still at higher risk of severe AD than those without hay fever, when asthma was included with other potential confounders in the analysis (OR = 2.42; 95%CI, 1.39 to 4.2, $p = 0.002$).

3.2.2.1.3.2 Child's asthma

Children who have had asthma have more severe disease than those who have never had asthma (OR = 1.95; 95%CI, 1.34 to 3.34, $p = 0.016$). This became statistically insignificant after adjusting for hay fever (OR = 1.67; 95%CI, 0.96 to 2.9, $p = 0.07$). The independent effect, therefore, was due to hay fever and not bronchial asthma, but with a reasonably tight 95%CI indicating that the data are consistent with the true odds ratio falling anywhere between these values.

If hay fever was not included amongst other potential confounders, children with AD who had asthma were still at statistically significant high risk of having severe AD (OR = 2.0; 95%CI, 1.1 to 3.6, $p = 0.021$) than those who never had asthma.

3.2.2.1.3.3Any atopic disease in the child

Children with any type of atopy, whether asthma or hay fever, were at a higher significant risk to have severe disease than those with no atopy at all (OR = 2.61; 95%CI, 1.61 to 4.24, $p < 0.001$). The relationships remained significant even after adjusting for potential confounders (OR = 2.86; 95%CI, 1.8 to 4.55, $p < 0.001$). Food was not independently associated with the exposure and outcome, so it was not considered as potential confounders.

3.2.2.1.4 Sex

Although there were more females in the urban population, sex distribution in general was approximately the same 65 (47%) males and 72 (53%) females (Table 24).

Table 24. Sex distribution by area of residence

Region	Male (%)	Female (%)	Total (%)
Urban	33 (40)	49 (60)	82 (60)
Rural	32 (58)	23 (42)	55 (40)
Total	65 (47)	72 (53)	137

Males are at a non-significant risk of severe disease than females (OR = 1.19; 95%CI, 0.72 to 1.97, $p = 0.49$), with reasonably tight confidence interval. This non-significant relationship with disease severity persisted even after adjusting for potential confounders (OR = 1.41; 95%CI, 0.83 to 2.42, $p = 0.2$). Because of the potential observer's bias, parents' assessment of disease severity in the questionnaire was used as the outcome of interest, however the relationship between sex and disease severity remained insignificant (OR = 0.80; 95%CI, 0.48 to 1.39, $p = 0.45$). Thus there was no evidence to suggest a significant difference in disease severity between males and females.

3.2.2.1.5 Birth weight

The mean birth weight was 3368 grams (SD 601) and the lowest and highest birth weights were 1361 and 4423 grams respectively. In order to facilitate analysis, birth weight was ranked into three categories: low (below 2.5 kilograms), average (between 2.5 and 4.0 kilograms), and more than average (more than 4.0 kilograms) as shown in Table 25. There were no data for 22 (16%) children regarding birth weight which were not included in Table 25.

Table 25. Ranked birth weight

Birth weight ranking	Number (%)
Less than 2500 grams (Low)	9 (8)
Between 2501 and 4000 grams (average)	92 (80)
More than 4000 grams (more than average)	14 (12)
Total	115

An ordered logistic regression model revealed no significant association between disease severity and low birth weight (less than 2500 grams versus more) before (OR = 1.37; 95%CI, 0.51 to 3.7, p = 0.53) and after adjusting for breast-feeding, gestational age, mother’s age when the child was born, social class, ethnic group, family size, area of residence, sex and age of onset (OR = 1.31; 95%CI, 0.45 to 3.9, p = 0.61).

3.2.2.1.6 Gestational age

The gestational ages of the premature group were 36 weeks in seven children, 35 weeks in one, 34 weeks in two, 33 weeks in two, and 32 weeks in one. Information about gestational age was missing in 14 (10%) children. The normal gestational age was taken as between 37 and 40 weeks inclusive. Premature and over dues were compared to this standard. Table

26 shows the ranked distribution of gestational age for 123 patients: premature, normal and over due.

Table 26. Ranked distribution of gestational age

Ranked gestational age	Number (%)
Premature (32-36 weeks)	13 (11)
Normal (37-40 weeks)	73 (59)
Over due (41-42 weeks)	37 (30)
Total	123

Premature children with eczema (36 weeks or less) have a slightly elevated risk of severe disease without reaching statistical significance (Table 27).

Table 27. Odds ratio for severe disease by gestational age

Gestational age	OR	95% CI	P value
Premature versus normal	1.26	0.4 to 3.96	0.69
Over due versus normal	0.62	0.35 to 1.08	0.09
Premature versus over due	2.0	0.62 to 6.54	0.24

OR; Odds Ratio. CI; Confidence Interval

Adjusting for the following confounding factors: birth weight, family size, age of mother and gender did not affect the outcome. On the other hand, children with eczema who were born later than 40 weeks (41 weeks or more), are at a lower insignificant risk of severe disease. However, when children born prematurely (36 weeks or less) compared with over due children (41 weeks or more), premature children still have an insignificant risk of severe disease (see Table 27).

Therefore neither birth weight nor gestational age was associated with severe disease, an association that remained insignificant after adjusting for potential confounders.

3.2.2.1.7 Family size

Figure 7 shows that 57 (42%) children had one sibling (a brother or a sister), 42 (31%) children had two brothers and/or sisters, 17 (12%) children had three or more brothers and/or sisters, and in 21 (15%) children the child was the only sibling in the family. As shown in the bar chart **(Figure 7)**, the distribution in both areas was almost the same. The mean number of children per household was 2.5 (SD 1.02).

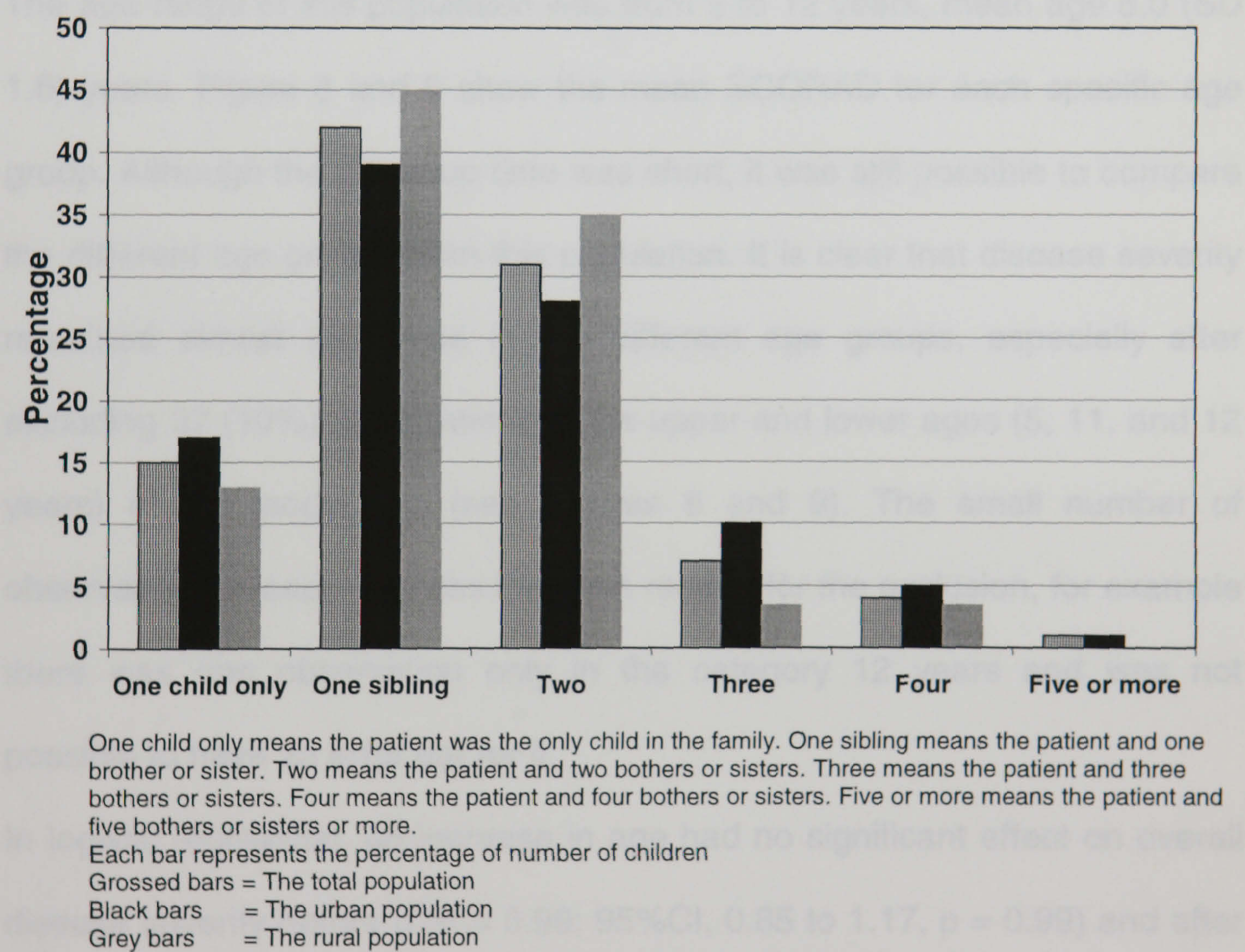


Figure 7. Percentage of sibling per area of residence and for the whole sample

An increase in the number of children has not been significantly associated with disease severity over time (OR = 1.02; 95%CI, 0.8 to 1.3, p = 0.87) and remained insignificant after adjusting for potential confounders. A binary variable was created by dividing the number of children in the house into greater than two children and two or less. The number (2) was chosen based

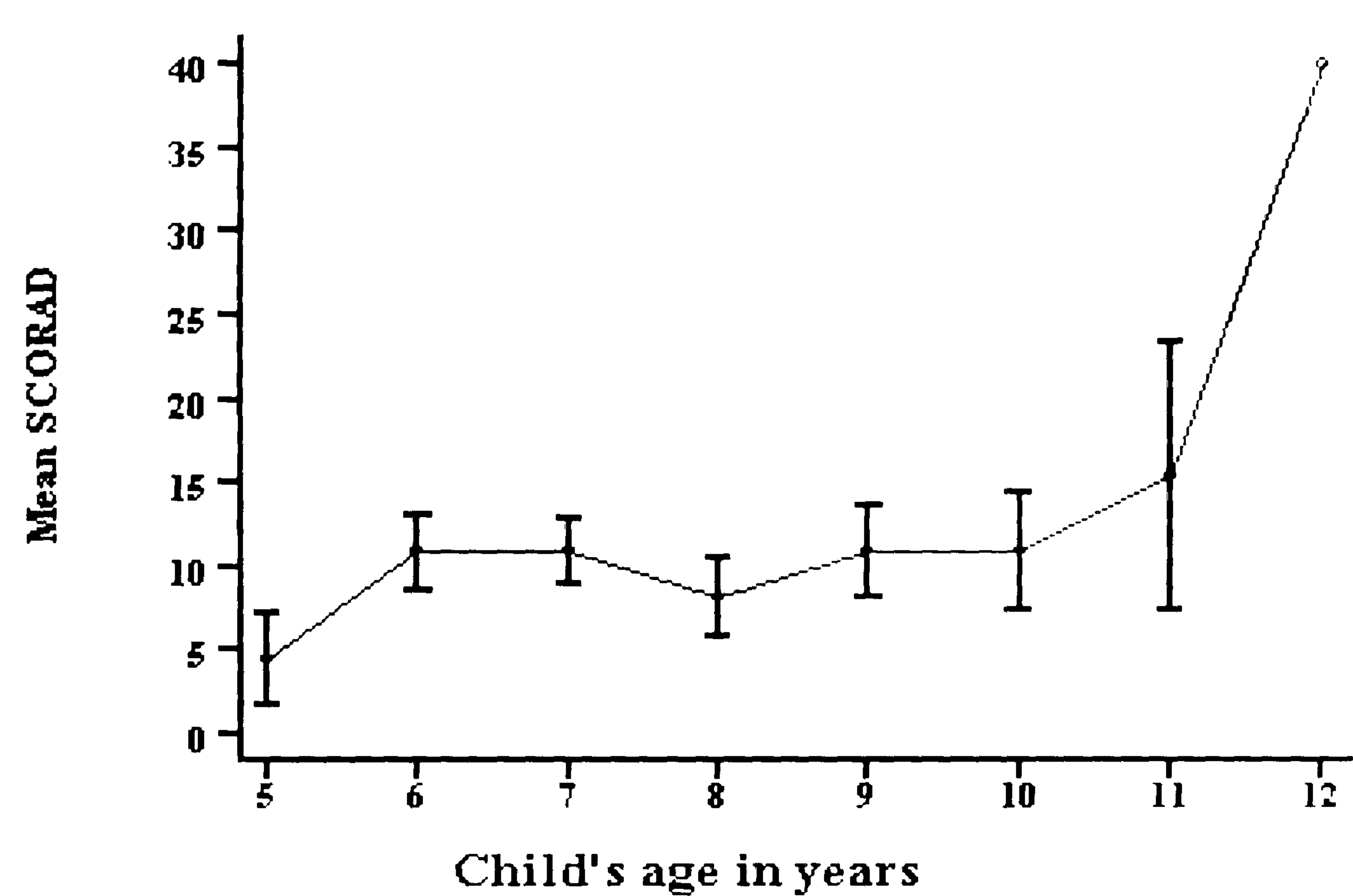
on the national average of 2.4 children rather than using the results of multiple statistical testing and would hopefully be meaningful to the reader. There was a non-significant increase in the risk of having severe disease in families with 2 children or less (OR = 1.2; 95%CI, 0.71 to 1.99, $p = 0.51$) and this remained insignificant after adjusting for potential confounders (OR = 1.1; 95%CI, 0.62 to 1.88, $p = 0.78$). Thus family size had no significant association with disease severity.

3.2.2.1.8 Child's age

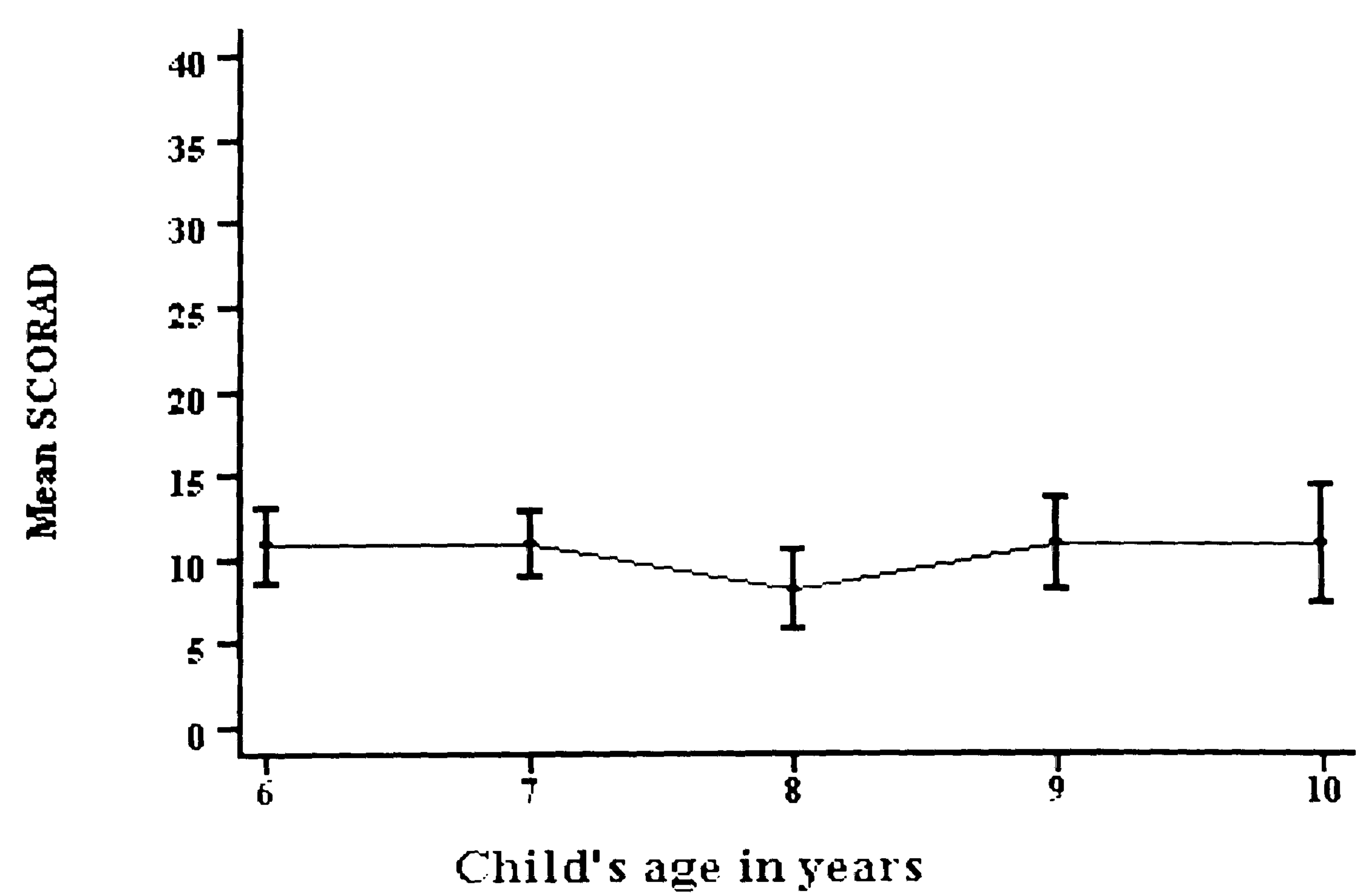
The age range of this population was from 5 to 12 years, mean age 8.0 (SD 1.6) years. Figure 8 and 9 show the mean SCORAD for each specific age group. Although the follow-up time was short, it was still possible to compare the different age group within this population. It is clear that disease severity remained almost the same in the different age groups, especially after excluding 37 (10%) observations in the upper and lower ages (5, 11, and 12 years) of this population (see Figures 8 and 9). The small number of observations in each age was the main reason for the exclusion, for example there was one observation only in the category 12 years and was not possible to have an error bar for it.

In logistic regression, an increase in age had no significant effect on overall disease severity before (OR = 0.99; 95%CI, 0.85 to 1.17, $p = 0.99$) and after controlling for potential confounders (OR = 0.98; 95%CI, 0.83 to 1.17, $p = 0.87$). When child's age was ranked into two categories (5-7 vs. 8-12 years), regression analysis showed that the older age group were at non-significant lower risk of having severe disease than younger age group (OR = 0.79; 95%CI, 0.49 to 1.25, $p = 0.31$). Nevertheless, there was a non-significant

relationship between child's age and disease severity according to an observer's assessment over two years.



Error bars = 95% Confidence interval
Figure 8. Mean SCORAD & 95%CI for each age group



Error bars = 95% Confidence interval
Figure 9. Mean SCORAD & 95%CI for each age group after excluding 37 (10%) observations for children aged 5, 11, and 12 years

3.2.2.1.9 Parental atopy

Table 28 shows atopic diseases in the parents and in their families. It is quite clear that there is more missing data about paternal than maternal atopy.

Table 28. Atopic diseases in mother, father and their families

Variable	Eczema (%)	Asthma (%)	Hay fever (%)	Atopy (%)
Maternal				
No	79 (58)	87 (63)	77 (56)	52 (38)
Yes	31 (22)	23 (17)	33 (24)	58 (42)
Missing	27 (20)	27 (20)	27 (20)	27 (20)
Paternal				
No	81 (59)	84 (61)	70 (51)	52 (38)
Yes	18 (13)	15 (11)	29 (21)	47 (34)
Missing	38 (28)	38 (28)	38 (28)	38 (28)
Mother's family				
No	67 (49)	61 (45)	67 (49)	40 (29)
Yes	40 (29)	44 (32)	40 (29)	67 (49)
Missing	30 (22)	32 (23)	30 (22)	30 (22)
Father's family				
No	73 (53)	72 (53)	84 (61)	55 (40)
Yes	27 (20)	28 (20)	16 (12)	45 (33)
Missing	37 (27)	37 (27)	37 (27)	37 (27)

3.2.2.1.9.1 Parents' Eczema

Mothers and fathers who had suffered from eczema were identified in 31 (22%) and 18 (13%) children respectively. In this population children with AD whose mother had suffered from eczema had a lower mean SCORAD than those whose mother had never suffered from eczema (Table 29). Paternal eczema produces an opposite trend. In an ordered logistic regression with the mean SCORAD as the outcome, children with a positive history of paternal eczema had a non-significantly higher risk of having severe disease than those whose father's had no eczema. On the other hand, children whose mother had eczema had a non-significant lower risk of severe disease than those whose mother's had no eczema (Table 29). This opposite parental effect remained insignificant after adjusting for breast-feeding, area

of residence, age at onset, ethnic group and social class (OR = 0.82; 95%CI, 0.43 to 1.58, p = 0.56 for maternal eczema, and OR = 1.31; 95%CI, 0.45 to 3.76, p = 0.5 for paternal eczema). However the number of children whom mothers had eczema (10 children) versus paternal eczema only (7 children) were too small to draw any conclusion.

Table 29. Mean SCORAD and Odds Ratio by parental eczema, asthma, or hay fever

Exposure	Mean SCORAD		OR	95% CI	P value
	Yes	No			
Maternal eczema	8.7	10.7	0.78	0.42 to 1.47	0.44
Paternal eczema	12.5	9.9	1.25	0.48 to 3.22	0.65
Maternal asthma	10.4	10.1	1.5	0.6 to 2.2	0.67
Paternal asthma	7.6	10.9	0.65	0.28 to 1.5	0.32
Maternal hay fever	12.8	9.2	1.9	0.95 to 3.8	0.07
Paternal hay fever	14.1	9.1	1.9	0.8 to 4.5	0.14
Maternal atopy	10.6	9.7	1.3	0.75 to 2.25	0.35
Paternal atopy	12.3	8.9	1.8	0.98 to 3.32	0.06

OR; Odds Ratio. CI; Confidence Interval

3.2.2.1.9.2 Parent’s asthma and/or hay fever

Parents’ asthma and/ or hay fever had a non-significant predictive value for AD severity (see Table 29). However, maternal hay fever had a marginally insignificant effect. All these factors were not considered for further analysis such as controlling for confounding effects because information bias regarding these factors was potentially high.

3.2.2.1.9.3Paternal and maternal atopy

Table 28 shows that 42% and 34% of children’s mothers and fathers were reported to be atopic. Children with atopic fathers are at a marginally significant higher risk to have severe disease than those whose fathers were not atopic (asthma, hay fever or eczema). Atopy in the mother showed the same trend with overlapping 95% confidence intervals (see Table 29). However, the small number of atopic mothers only versus atopic fathers did not allow direct comparison between the two variables.

3.2.2.1.10 Atopic diseases in siblings (brothers and sisters)

Siblings of 41 (30%), 29 (21%), and 20 (14%) children had suffered from eczema, asthma, and hay fever respectively. In ordered logistic regression, atopy in sibling has no significant association with disease severity (see Table 30). The statistically insignificant results and potential risk of bias due to high percentage (26%) of missing values made considering these finding for further statistical analysis inconclusive and will not be discussed further.

Table 30. Number of sibling (brothers and sisters) with and without atopic disease and the odds ratio for severe AD with 95%CI

Exposure	Number (%)			OR	95%CI	P value
	Yes	No	Missing			
Eczema	41 (30)	61 (44)	35 (26)	0.84	0.45 to 1.54	0.56
Asthma	29 (21)	73 (53)	35 (26)	1.59	0.74 to 3.44	0.23
Hay fever	20 (14)	82 (60)	35 (26)	1.78	0.83 to 3.73	0.14

OR; Odds Ratio. CI; Confidence Interval

3.2.2.1.11 Summary of intrinsic factors

- Children with atopic dermatitis starting during the first year of life are almost two times more likely to have severe disease than those with eczema starting later. Early onset AD is an important predictor of more severe disease later in life (5-12 years).
- Children with black skin who have AD are about six times more likely to have severe disease.
- Reliance on erythema scores can mask severe disease in black children.
A point that should always be considered in measuring disease severity in patients with pigmented skin
- Children with atopic dermatitis who have other atopic diseases (asthma and/or hay fever) were at a higher significant risk of severe disease than those who had not had any atopic diseases.
- Family size, sex, birth weight, gestational age, child's age, any atopy (hay fever, asthma, or eczema) in parents, and any atopy in siblings have no significant association with disease severity.

3.2.2.2 Extrinsic factors as the exposure

3.2.2.2.1 Area of residence

The study included two populations from two different areas of residence (urban/rural) in the UK. Eighty-two (60%) children living in south London represented the urban population and 55 (40%) children resident in mid Wales represented the rural population.

Children with atopic dermatitis in south London have a significantly higher risk of severe disease than their counterparts in mid Wales (OR = 1.87; 95%CI, 1.12 to 3.11, p value = 0.017). This difference remained statistically significant after adjusting for sex, family size, social class, ethnic group, and child's age (OR = 2.15; 95% CI, 1.12 to 4.1, p value = 0.021).

However, one should bear in mind observer bias, as the investigator was aware where the cases came from, urban or rural area. So, was there a chance that the urban patients could have been given a high score? To determine this, the observer scores (SCORAD-D) were excluded and parents' scores (subjective symptoms) were used on their own, which was significantly correlated to observer's scores (SCORAD-D) at each visit (see Table 16). The odds ratio increased to 2.79 (95%CI, 1.68 to 4.5, $p < 0.001$) for the total subjective symptom score, 2.6 (95%CI, 1.59 to 4.2, $p < 0.001$) for pruritus and 3.65 (95%CI, 1.85 to 7.1, $p < 0.001$) for sleep loss. The observer appeared to have no effect on this scoring as it was completely scored by the parents on a visual analogue scale. However, intra-observer variability cannot totally be excluded, as the investigator could not be blinded for area of residency. The risk of severe disease in the urban group remained highly significant even when the SCORAD and its components were excluded from

the analysis and parents' assessment of disease severity on 0 to 10 analogue scale was used in its own (OR = 2.78; 95%CI. 1.65 to 4.69, $p < 0.001$).

In summary, children who live in the urban area have more severe atopic dermatitis than their white counterparts living in a rural area. This significant difference remained the same when three different way of severity assessment were used.

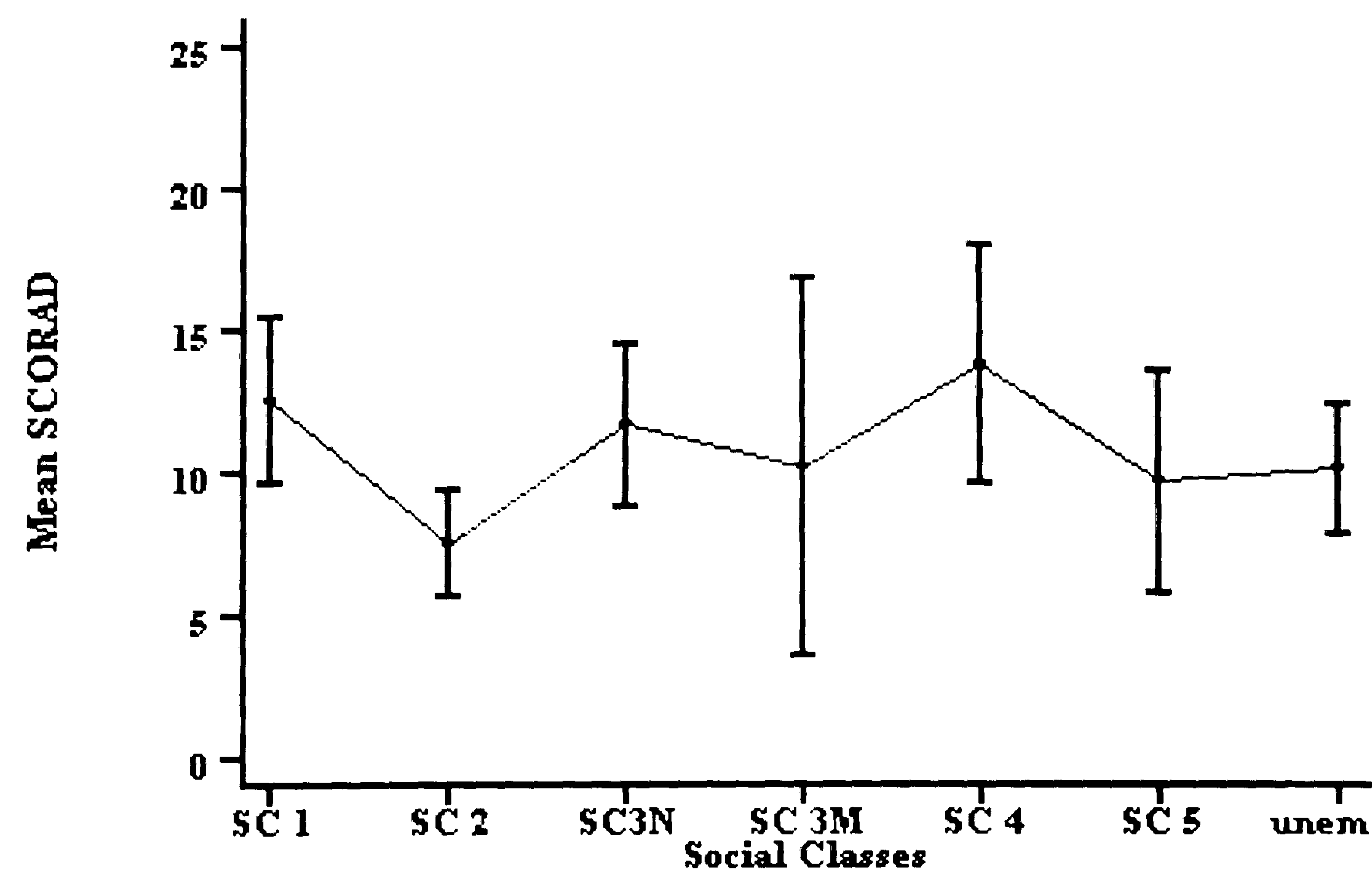
3.2.2.2.2 Social class

Children were classified by the father's job on recruitment; the mother's job was used with single mothers or where the father was unemployed and she was employed. The social classes ranking was formed according to the Registrar General classification (Leete and Fox., 1977). For 75 (55%) children, parents were ranked in social classes I, II and III-non-manual, and 32 (23%) children ranked in social classes III-manual, IV, and V. Parents of 30 (22%) children were unemployed, of these 27 (20%) children were in the urban area (see Table 31). These figures represent a wide variation of social classes. In this population the unemployment rate was higher in the urban than rural areas (33% versus 5%). On the other hand there were more children from social class II in the rural area than the urban; 34% versus 13% respectively, because of the farming industry in the area. Apart from social class II and unemployment, the distributions of other social classes were almost the same in both areas.

Table 31. Social class distribution by area of residency and for the whole sample

Social class	Urban (%)	Rural (%)	Whole population (%)
One	9 (11)	7 (13)	16 (12)
Two	11 (13)	19 (34)	30 (22)
Three non-manual	17 (21)	12 (22)	29 (21)
manual	2 (3)	1 (2)	3 (2)
Four	11 (13)	6 (11)	17 (12)
Five	5 (6)	7 (13)	12 (9)
Unemployed	27 (33)	3 (5)	30 (22)

Figure 10 shows no gradient trend in the mean SCORAD from high to low social classes. Children in social class four have the highest mean score and children in social class two have the lowest mean score. The small number of subjects in social class three-manual reflected by the wide confidence interval in Figure 10.



SC1 = Social class 1, SC2 = Social class 2, SC3N = Social class 3 Non-manual, SC3M = Social class 3 Manual, SC4 = Social class 4, SC5 = Social class 5, Unem = unemployment
Error bars = 95% Confidence interval

Figure 10. Mean SCORAD and 95%CI per each social class

Children in social classes one and two were compared with those from other social classes. There was no significant difference in disease severity between children in social class I and II, and those in other social classes (OR = 1.02; 95%CI, 0.57 to 1.8, p = 0.95). The effect remained insignificant after adjusting for potential confounders and therefore social class had no significant association with disease severity.

3.2.2.2.3 Food

Parents of 36 (27%) children reported that some kind of food made their child’s eczema worse and parents of 60 (44%) children reported no food effect, while parents of 39 (29%) children did not know whether food had an effect or not. Data were missing in 2 children (Table 32).

Table 32. Eczema and food with severity scores

Eczema gets worse by food	Number (%)	SCORAD		SCORAD-D	
		Mean (SD)	Median (95%CI)	Mean (SD)	Median (95%CI)
No	60 (44)	10.0 (10.3)	8 (7 to 10)	7.2 (8.3)	5 (4 to 7)
Yes	36 (27)	15.2 (13.3)	12 (9 to 17)	10.4 (10.8)	8 (7 to 11)
DK	39 (29)	7.7 (9.5)	4 (3 to 7)	4.9 (7.2)	0 (0 to 4)

DK; Don't Know

Those who reported food effects mentioned the following foods as being responsible for their children’s eczema exacerbation; dairy products (including milk, cheese, yoghurt), eggs, fish (including sardines), chocolate, coloured drinks (including squash and cola), crisps and snacks, fresh fruit (includes apple, satsuma, citrus fruits, strawberries, banana, orange), sweets, and other (pork, yeast, fried food, porridge oats, raw potato). Most of the foods already mentioned have potential antigenic properties.

The mean SCORAD and SCORAD-D was higher for those who answered “yes” than those who answered “no”, and the lowest score was for those who answered “don’t know”. The median scores had the same trend (Table 32). Answering “yes” to the question about food (question number 32 in the recruitment questionnaire) was associated with a higher risk of severe atopic dermatitis than answering “no” (OR = 2.1; 95%CI, 1.08 to 4.07, $p = 0.029$). It became statistically insignificant after controlling for potential confounders (OR = 1.9; 95%CI, 0.89 to 4.2, $p = 0.09$). Therefore some kinds of food were associated with increased disease severity that became statistically insignificant after adjusting for potential confounders.

3.2.2.2.4 Wool

In this population 59 (43%) children had no reaction to wool and 68 (50%) children had reacted to wool and data were missing in 10 (7%) children who were not included in the previous descriptive statistics. Children with AD who reacted to wool were almost two times (OR = 1.8; 95%CI, 1.06 to 2.98, $p = 0.03$) more likely to have severe disease than those who do not. The relationships remained significant even after excluding subjective symptoms scores (OR = 1.73; 95%CI, 1.02 to 2.95, $p = 0.043$). However, this became statistically insignificant after adjusting for area of residence (OR = 1.45; 95%CI, 0.83 to 2.54, $p = 0.19$).

Children who had reacted to wool were about two times more likely of having severe atopic dermatitis than those who had not reacted; an association that became statistically insignificant after adjusting for area of residence.

3.2.2.2.5 Breast feeding

Forty (29.6%) children received no breastfeeding at all, 40 (29.6%) received breast-feeding for 3 months or less, 55 (40.8%) children were breast fed for more than three months, and data were missing in 2 children. There was no gradient trend in disease severity between the frequencies of breast-feeding, see Table 33.

Table 33. Breast feeding distribution and mean SCORAD

Frequency of feeding	Number (%)	Mean SCORAD (SD)
No feeding	40 (29.6)	9.6 (11.6)
3 months or less	40 (29.6)	11.9 (11.9)
More than 3 months	55 (40.8)	10.7 (10.6)

No significant association was seen between breast-feeding (expressed in the form of a yes/no binomial variable) and total severity score before and after adjusting for potential confounders (Table 34). Positive history of hay fever and/or asthma were not included in the adjustment because their effects could be part of the outcome and therefore were not independently related to exposure and outcome.

When the duration of breast-feeding was divided into two categories (Breast feeding for 3 months or less versus more than 3 months), no significant association was detected between the duration of breast-feeding and disease severity, before and after adjusting for potential confounders (Table 34).

Table 34. Odds ratio (OR) of severe disease for breast feeding before and after adjusting for potential confounders

Breast feeding for ...	Crude OR (95%CI)	P	Adjusted OR (95%CI)	P
3 months or less versus none (Yes/No)	1.36 (0.78 to 2.4)	0.28	1.39 (0.73 to 2.65)	0.31
More than 3 months versus 3 months or less	0.93 (0.51 to 1.7)	0.82	0.96 (0.52 to 1.78)	0.91

P; p-value. OR; Odds Ratio. CI; Confidence Interval

3.2.2.2.6 Other extrinsic factors

Frequency of household vacuuming, frequency of mattress vacuuming, presence of fitted carpets, type of heating, having pets, site of the house, distance of the house from the main road, or trees in the front of the house all had no significant effect on disease severity and therefore this will not be discussed any further.

3.2.2.2.7 Summary of extrinsic factors

- Children who live in the urban area had a higher significant risk of severe disease than their counterparts who live in the rural area.
- Children who had reacted to wool were at a significant higher risk of severe disease than those who had not reacted and this became insignificant after adjusting for the area of residence.
- Children whom their parents reported that food had made the eczema worse had the same trend as reaction to wool.
- Social class and breastfeeding were not significantly associated with disease severity.

3.2.3 Independent risk factors for AD severity over time

When urban area, age at onset, asthma and hay fever were only included in ordered logistic regression, the effect of each of these factors remained independently and significantly related to disease severity (Table 35).

Table 35. Odds ratio for severe atopic dermatitis by area of residence, age at onset, asthma, hay fever, child’s atopy, and black skin

Risk factor	OR	95% CI	P value
Urban area	1.95	1.17 to 3.23	0.01
Onset during the first year of life	1.9	1.15 to 3.13	0.013
Child’s asthma	1.8	1.02 to 3.18	0.042
Child’s hay fever	2.2	1.24 to 3.83	0.009
Child’s atopy	2.7	1.66 to 4.4	0.000
Black skin	5.2	1.75 to 15.2	0.003

OR; Odds ratio; CI; Confidence Interval

The risk remained independently significant for all these factors when history of asthma and/or hay fever considered as positive history of atopy in the children and when black children, atopy in child, urban area, and age of onset were included and adjusting for erythema scores. These factors retained their significant and independent association with disease severity over time.

3.3 Section 3: Quality of life

Quality of life in the child and family was quantified by two different questionnaires on two occasions (March and October 1999). Social class, ethnic background, child's age, family size, area of residence (urban/rural) and sex were controlled for and referred to as potential confounders.

3.3.1 The family's quality of life

The DFI was used to assess the impact of children's eczema on their family and the higher the score the worse the impact (Lawson, *et al*, 1998).

3.3.1.1 The total DFI at visits one and two

The numbers of children presented in the summary statistics are those who attended each quality of life visit. For instance 116 and 120 children attended the first and second QOL assessment visits respectively. Of 116 attending the first visit, 106 attended the second visit. The percentage and mean DFI score for the two groups are shown in Table 36.

Table 36. Percentage and mean DFI scores for 106 children attending both visits and total number at each visit

DFI	Number of children seen per each visit			
	Visit one		Visit two	
	116	106	120	106
Percentage affected (scored more then zero on DFI)	45%	45%	33%	36%
Mean score	2.32	2.39	1.88	1.87

Table 36 shows clearly that the 14 children who attended the second but not the first visit, did not have any substantial effect on the mean DFI score nor on the percentage of those who scored more than zero on DFI. Therefore,

the total number will be included in the cross sectional description and excluded in comparison between the two visits.

The DFI was filled in by the mother in 115 (99%) children and by the father in one child only during the first quality of life assessment visit (March 1999). On the final visit used to assess the family's quality of life (October 1999), the DFI was completed by the mother in 119 (99%) children and by the father in one child. Parents of 111 (96%) children with a mean DFI score 2.4 (SD 4.3) and parents of 118 (98%) children with a mean DFI score of 1.8 (SD 4.3) had answered all the 10 questions of the DFI at visits one and two respectively. The initial mean of DFI for the total number of 116 subjects was 2.3 (SD 4.3) and six months later the mean final DFI for 120 subjects was 1.9 (SD 4.3). It was clear that there were no significant differences between those who answered all the questions and those who did not complete the whole questionnaire. It was therefore decided to include the scores for the total number and giving zero scores for missing answers.

The medians of DFI for the first and second visits were 0 (upper quartile 3, lower quartile 0) and 0 (upper quartile 1, lower quartile 0) respectively, representing a non-significant improvement perceived by the parents ($p=0.1$).

Although the maximum score of the DFI is 30, in this study the maximum scores were 21 and 25 at the first and second visit respectively. Families' quality of life was affected in the household of 52 (45%) and 40 (33%) children during the first and final visits respectively. In other words, these figures show the percentage for those who scored more than zero on the DFI at each visit. Figure 11 shows the percentage per aspect of families' life

affected by the children's eczema for 116 and 120 children attending visits one and two respectively.

The total DFI scores were significantly correlated with SCORAD-D at visits one ($r= 0.19$, $p = 0.042$) and two ($r= 0.32$, $p < 0.001$). In multiple regression analysis and after controlling for potential confounders, each unit increase in SCORAD-D led to a 0.21 unit increase in DFI (95%CI, 0.07 to 0.36, $p = 0.004$) during the initial visit. On the final visit each unit increase in SCORAD-D was significantly associated with a 0.38 unit increase in DFI (95%CI, 0.16 to 0.59, $p = 0.001$). In other word this mean that a 10 units increase in the SCORAD-D was associated with 3.8 units increase in the DFI at visit two.

The DFI was also significantly correlated to the parents' grading of diseases status on a 0 to 10 scale at the first ($r= 0.51$, $p < 0.001$) and second ($r= 0.49$, $p < 0.001$) visits. This shows that AD severity had a direct impact on family's quality of life and also reflects the internal consistency of the parents' evaluation.

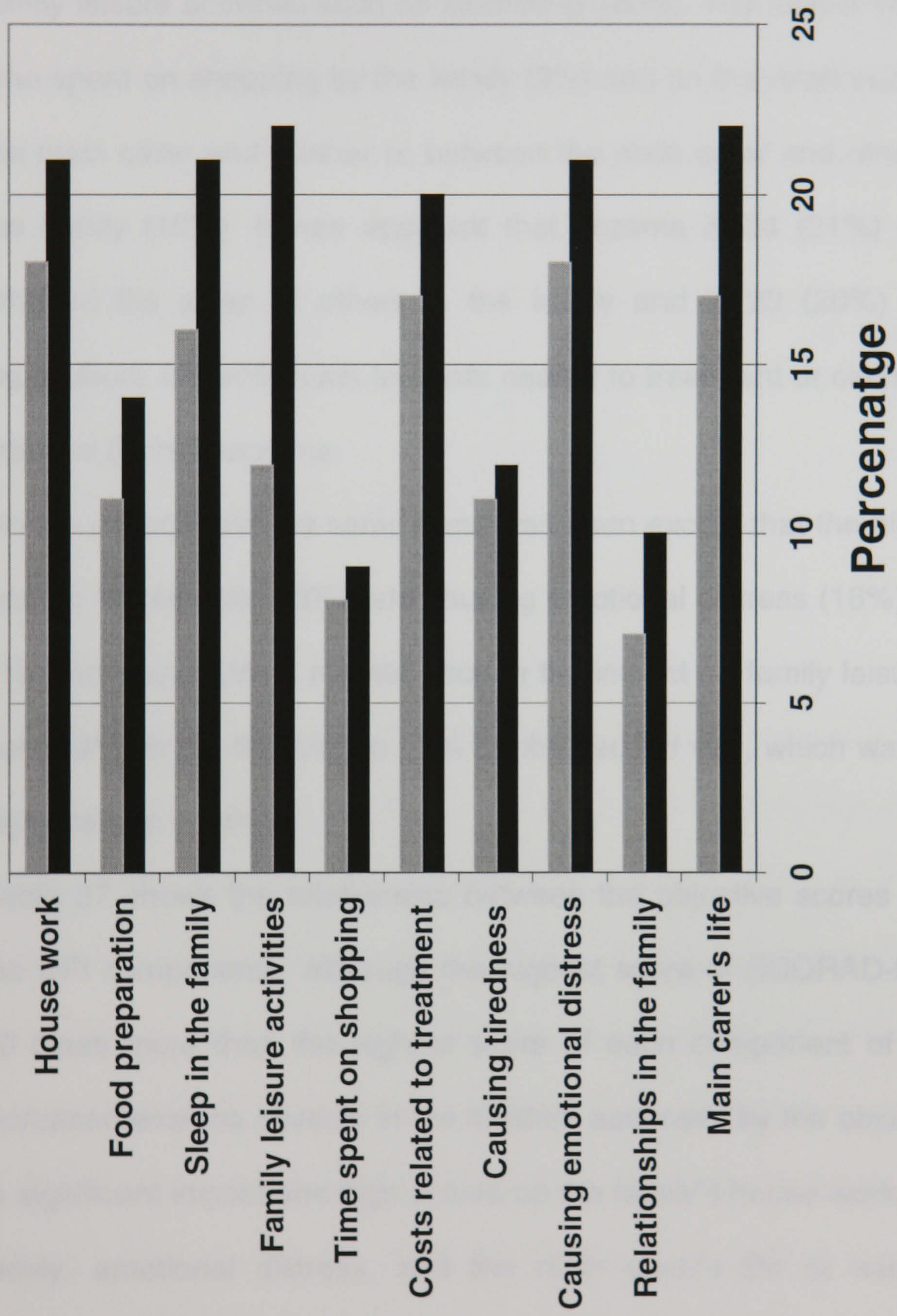


Figure 11. Percentage per each item of the DFI on visits 1 and 2 for 116 and 120 children respectively

3.3.1.2 Each aspect of the DFI on visit one and two

The 10 items shown in Figure 11 form the total DFI scores. During the first visit for example, the highest impact was on the main carer's life (22%) and family leisure activities such as swimming (22%). The lowest impact was on time spent on shopping by the family (9%) and on the relationships between the main carer and partner or between the main carer and other children in the family (10%). It was apparent that eczema in 24 (21%) children had affected the sleep of others in the family and in 23 (20%) children the expenditure of family such as costs related to treatment or clothes had been affected by their eczema.

On the second visit the same trend was seen except that the highest impact was on housework (18%) and causing emotional distress (18%) (see Figure 11). There was also a marked drop in the impact on family leisure activities, from 22% on the first visit to 12% on the second visit, which was statistically significant ($p = 0.013$).

Table 37 shows the relationship between the objective scores and each of the DFI components. Although the highest score of SCORAD-D was about 20 times more than the highest score of each component of the DFI, an increased eczema severity in the children assessed by the observer had led to significant impact and high scores on the family's house work, sleep in the family, emotional distress, and the main carer's life at each visit. The relationship between eczema severity and causing tiredness was significant at the first visit but not at the second visit.

Table 37. Relationships between disease severity (SCORAD-D) and the DFI components

The DFI components	Visit One			Visit Two		
	R*	95%CI	P value	R*	95%CI	P value
House work	0.06	0.01 to 0.11	0.023	0.08	0.001 to 0.15	0.043
Food preparation	0.01	-0.05 to 0.06	0.75	0.07	-0.05 to 0.19	0.23
Sleep in the family	0.05	0.004 to 0.089	0.032	0.09	0.02 to 0.17	0.017
Family leisure activities	0.04	-0.01 to 0.08	0.09	0.07	-0.01 to 0.15	0.09
Time spent on shopping	0.02	-0.06 to 0.09	0.59	0.05	-0.05 to 0.15	0.3
Costs related to treatment	0.001	-0.05 to 0.05	0.96	0.06	-0.004 to 0.13	0.07
Causing tiredness	0.09	0.2 to 0.15	0.015	0.08	-0.02 to 0.17	0.1
Causing emotional distress	0.05	0.003 to 0.1	0.037	0.11	0.05 to 0.17	0.001
Relationships in the family	0.06	-0.01 to 0.12	0.09	0.11	-0.01 to 0.23	0.07
Main carer's life	0.06	0.01 to .011	0.017	0.1	0.04 to 0.17	0.003

Bold; Statistically significant results (p value less than 0.05).
CI; Confidence Interval. R*; Regression coefficient

3.3.1.3 The DFI at visits one and two by site

The following findings are for all children seen in visits one and two (116 and 120 children), in which the mean DFI scores for 5 body regions (Face and neck, chest and abdomen, upper limb, back, and lower limb) were considered. The mean and median DFI scores were compared between sites with visible eczema and those free of eczema and between each other. Tables 38 and 39 show quite clearly that visible eczema at any site of the body had more impact on family’s quality of life than areas free of eczema at any visit. For instance, the mean DFI at visit one was about three times more in children with visible eczema on the back than those without any visible eczema. Eczema on the back had the highest impact on family’s quality of life 4.9 (SD 5.7), which perhaps due to large surface area of the back. Visible eczema on the other sites of the body had a lower mean score than visible eczema on the back [chest and abdomen 4.5 (SD 6.0), face and neck 3.3

(SD 5.2), upper limb 3.1 (SD 4.5) and lower limb 2.9 (SD 4.5)]. Visible eczema during the second visit nearly had the same trend, except eczema on the chest and abdomen that had a higher impact than on the back (see Table 39). This reflects the crude sensitivity of the DFI to visible eczema and the ability of DFI to pick up a higher score when there was visible eczema. Statistical tests were not carried out because it was very difficult to control for the effect of other areas involved.

Table 38. Number of site involved with median and mean values for the DFI score (95%CI) per each visible eczema on each site of the body at the first quality of life assessment’s visit for 116 children

Site involved	Number of children with visible eczema (Median DFI1)		Mean DFI1 (95%CI) according to visible eczema per site	
	Yes	No	Yes (95%CI)	No (95%CI)
Back	18 (2.5)	98 (0)	4.9 (2.1 to 7.8)	1.8 (1.1 to 2.6)
Chest and abdomen	14 (2)	102 (0)	4.5 (1.0 to 8.0)	2.0 (1.3 to 2.8)
Face and neck	23 (1)	93 (0)	3.3 (1.0 to 5.5)	2.1 (1.3 to 2.9)
Upper limb	56 (1)	60 (0)	3.1 (1.9 to 4.3)	1.6 (0.6 to 2.6)
Lower limb	42 (1)	74 (0)	2.9 (1.9 to 4.3)	2.0 (1.1 to 3.0)

CI; Confidence Interval

Table 39. Number of site involved with median and mean values for the DFI score (95%CI) per each visible eczema on each site of the body at the second quality of life assessment’s visit for 120 children

Site involved	Number of children with visible eczema (Median DFI2)		Mean DFI2 (95%CI) according to visible eczema per site	
	Yes	No	Yes (95%CI)	No (95%CI)
Chest and abdomen	19 (1)	101 (0)	5.0 (1.3 to 8.7)	1.3 (0.7 to 1.9)
Back	23 (1)	97 (0)	4.7 (1.5 to 7.9)	1.2 (0.6 to 1.8)
Face and neck	18 (1)	102 (0)	3.8 (0.6 to7.1)	1.5 (0.8 to 2.3)
Lower limb	38 (1)	82 (0)	3.6 (1.7 to5.4)	1.1 (0.4 to 1.8)
Upper limb	44 (1)	76 (0)	3.2 (1.4 to 4.9)	1.1 (0.4 to 1.9)

CI; Confidence Interval

3.3.1.4 Changes in DFI and SCORAD-D scores over 6 months

The results from parents of 106 children (53 females) who completed the DFI in both visits are reported here. The children mean age was 7.9 and 8.4 years at the initial and final visits respectively. Family quality of life was affected in 54 (51%) children on at least one visit - 48 (45%) at the first visit and 38 (36%) six months latter. The initial mean of DFI for 106 subjects was 2.4 (SD 4.4). Six months later the mean final DFI was 1.9 (SD 4.2), representing a non-significant improvement perceived by the parents ($p=0.1$). Age, sex, family size, location and social class were not significantly related to changes in DFI. The initial mean of SCORAD-D for 106 children was 8.2 (SD 10.2) and six months later the mean final SCORAD-D was 7.7 (SD 8.7), representing a non-significant improvement documented by the study investigator ($p = 0.74$), which was expected in an observational study of mostly mild eczema cases.

The mean change in DFI was -0.5 (SD: 3.55), range -21 to 11 and in SCORAD-D was -0.5 (SD: 8.6), range -22 to 21. Of 106 children who attended both visits, 54 (51%) children were included in interval regression analysis because their eczema had affected their families' life. In other words, the parents scored more than zero on the DFI on at least one occasion. In multiple regression analysis, each unit change in SCORAD-D was associated with a 0.17 (95%CI, 0.06 to 0.29, $p = 0.002$) unit change in family quality of life. After adjusting for potential confounders each unit change in SCORAD-D led to a 0.16 (95%CI, 0.04 to 0.27, $p = 0.008$) unit change in DFI. Therefore, change in the DFI was significantly associated with change in the SCORAD-D.

3.3.1.5 Changes in the DFI Components and SCORAD-D over 6 months

Figure 11 shows the percentage per aspect of family’s life affected by their children’s eczema at each visit for all children who attending visit one and two. Changes in SCORAD-D were investigated for relation to each component of the DFI for those who attended both visits.

Examination of the relation between changes in each of the DFI components and in SCORAD-D revealed that the strongest and significant associations, although small, were seen in changes in the impact of eczema on family leisure activities such as swimming ($p = 0.002$) and causing tiredness or exhaustion on the child’s parents ($p < 0.001$), see Table 40. The significant relation between changes in disease severity and changes in the impact of eczema on family leisure activities persisted after controlling for potential confounders ($R = 0.04$; 95%CI, 0.01 to 0.06, $p = 0.002$). Change in “causing tiredness or exhaustion” also remain significantly related to changes in SCORAD-D after adjusting for potential confounders with narrower 95% confidence interval ($R = 0.03$; 95%CI, 0.03 to 0.04, $p < 0.001$). Relation between change in SCORAD-D and other components of the DFI were weak and not significant (Table 40).

Table 40. Relation between change in SCORAD-D scores and change in each components of the DFI

Change in the	Change in SCORAD-D		
	R	95%CI	P value
House work	-0.01	-0.05 to 0.03	0.57
Food preparation	-0.01	-0.07 to 0.05	0.82
Sleep in the family	0.01	-0.03 to 0.05	0.73
Family leisure activities	0.04	0.02 to 0.07	0.002
Time spent on shopping*	*96 and 98 of the 106 scored zero		
Costs related to treatment	0.01	-0.01 to 0.04	0.21
Causing tiredness	0.04	0.03 to 0.05	< 0.001
Causing emotional distress	0.03	-0.01 to 0.06	0.12
Relationships in the family*	*94 and 99 of the 106 scored zero		
Main carer's life	0.01	-0.02 to 0.04	0.37

*Large number of zero scores each visit so interval regression analysis was not possible
Bold; statistical significant. R; Regression coefficient. CI; Confidence Interval

3.3.1.6 Summary of the family's quality of life

- Family's quality of life was affected in the household of 45% and 33% of children on the first and second visits respectively, a finding that provide an evidence for the burden caused by mostly mild AD.
- There is a positive effect of increased disease severity on DFI scores. It implies that increased severity can lead to impairment in family's quality of life. The ultimate outcome of this provides a construct validity of the DFI in a community-based study.
- Changes in DFI scores were significantly correlated with changes in disease severity scores before and after adjusting for potential confounders.
- The DFI as a tool for assessing the impact of childhood atopic dermatitis on the family's quality of life was able to detect higher scores for the DFI when there is visible eczema than when there is no eczema seen. A finding that reflects the DFI crude validity.
- Scores in the questions concerning the main carer's life, house work, sleep in the family, and causing emotional distress were significantly correlated to the observer's scores of diseases severity at each visit.
- In conclusion, increased atopic dermatitis severity in children had led to increased impairment of their families' quality of life. The DFI was a practical tool to assess the impact of children's eczema on their family in a community-based study with mostly mild disease.

3.3.2 The children’s quality of life

3.3.2.1 Age and completion of the CDLQI on visits one and two

The CDLQI was used to quantify the impact of AD on the children’s life (Lewis-Jones and Finlay., 1995). In total 116 and 120 children attended the first and second quality of life assessment visits respectively. At visit one (March 1999), 78 (67%) children were able to complete the CDLQI, mean age 8.6 years, [44 (56%) females and 34 males], while 38 (33%) were unable to complete the CDLQI mean age 6.5 years, [16 (42%) females and 22 males]. On the final visit (October 1999), 90 (75%) children were able to complete the CDLQI, mean age 9.0 years, [52 (58%) females and 38 males], while 30 (25%) children were unable to complete the CDLQI mean age 7.1 years, [10 (33%) females and 20 males]. Seven children of the 38, who did not complete the CDLQI on the first visit, had completed it on the final visit. These 7 children were not included in the analysis.

On the first visit, the mean age of children who were unable to complete the CDLQI (6.5 years) was lower than those who completed the questionnaire (8.6 years), and on the second visit, the same trend was seen (7.1 and 8.9 years). There were also more males among those who were unable to complete the CDLQI (16 female and 22 male), despite higher number of females on each visit. Inability of the child to read without the help of parents was the main reason for not completing the CDLQI, even though other reasons cannot totally be excluded. Table 41 shows that all children aged 9 or more were able to complete the CDLQI, except one child who was unable to complete it. He was unable to read according to his mother. He fulfilled the

UK diagnostic criteria, had a visible eczema on visit one, and had cleared on the final visit.

Table 41. Children age and completion of the CDLQI on visits one and two

Children's age	Visit One		Visit Two	
	Completing the CDLQI		Completing the CDLQI	
	Yes (%)	No (%)	Yes (%)	No (%)
6 years	5 (18)	23 (82)	1 (20)	4 (80)
7 years	16 (62)	10 (38)	16 (44)	20 (56)
8 years	16 (80)	4 (20)	17 (77)	5 (23)
9 years	18 (100)	0 (0)	21 (100)	0 (0)
10 years	14 (93)	1 (7)	17 (94)	1 (6)
11 years	9 (100)	0 (0)	17 (100)	0 (0)
12 years	None	None	1 (100)	0 (0)
Total	78	38	90	30

Results that were shown in Table 41 raise a question about applicability of the CDLQI in assessment of quality of life in children aged 7 years or less. The literacy level varies from one child to another and social class may have an effect as well. However, there was insignificant difference between those who completed the CDLQI and those who did not in factors such as social class, ethnic background, and family size.

3.3.2.2 The CDLQI on both visits by gender

Males had a higher mean score than females on the first visit (4.66 vs 4.26), but on the second visit males and females almost had the same mean score (3.15 vs 3.16). The differences in the total CDLQI between males and females was not statistically significant on both visits ($p = 0.35$ and 0.3 respectively), as well as in each component of the CDLQI, except teasing scores on visit two.

Figures 12 and 13 show the mean scores of each component of the CDLQI for 71 males and females attending both visits. There was no significant difference between each components of the CDLQI except for teasing scores. During the second visit, males had a higher mean score for teasing (0.31) than females (0.13), which was statistically significant ($p = 0.021$). While on the first visit, the mean score for teasing was higher in females (0.26) than males (0.24), but was statistically insignificant ($p = 0.41$). Also, there was no evidence of any significant correlation between teasing scores of both sex and any components of the objective SCORAD (extent, total intensity, erythema, oozing, oedema/papulation, excoriation, and lichenification) on any visit. However, male scores on the CDLQI had a stronger association with disease severity than females (see Table 42).

Table 42. Correlation between the CDLQI and SCORAD by sex

Sex	Visit One		Visit Two	
	<i>R</i>	P value	<i>r</i>	P value
Male	0.56	< 0.001	0.66	< 0.001
Female	0.39	0.002	0.45	< 0.001

r, correlation coefficient

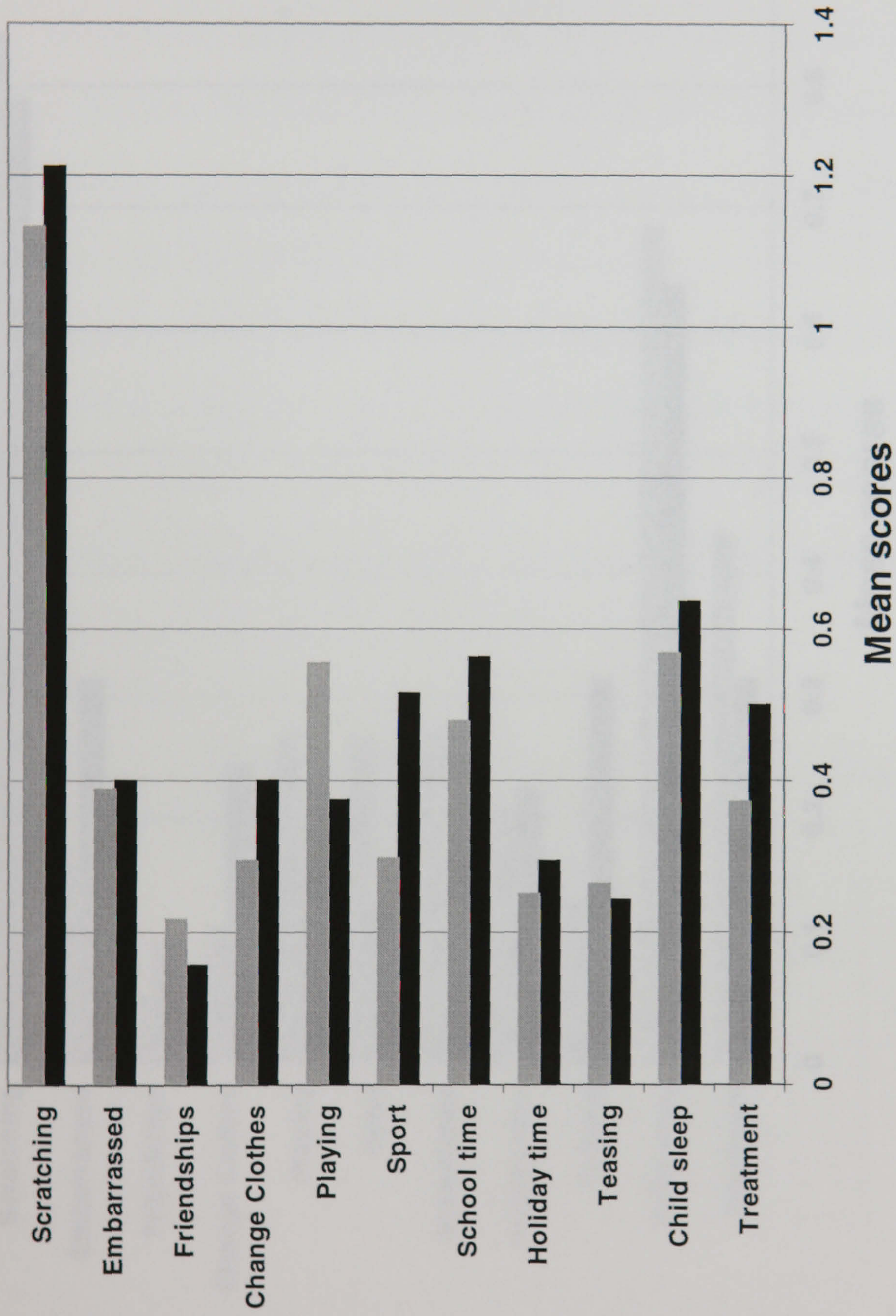


Figure 12. Mean scores of the CDLQI components for 71 males and females on the first visit

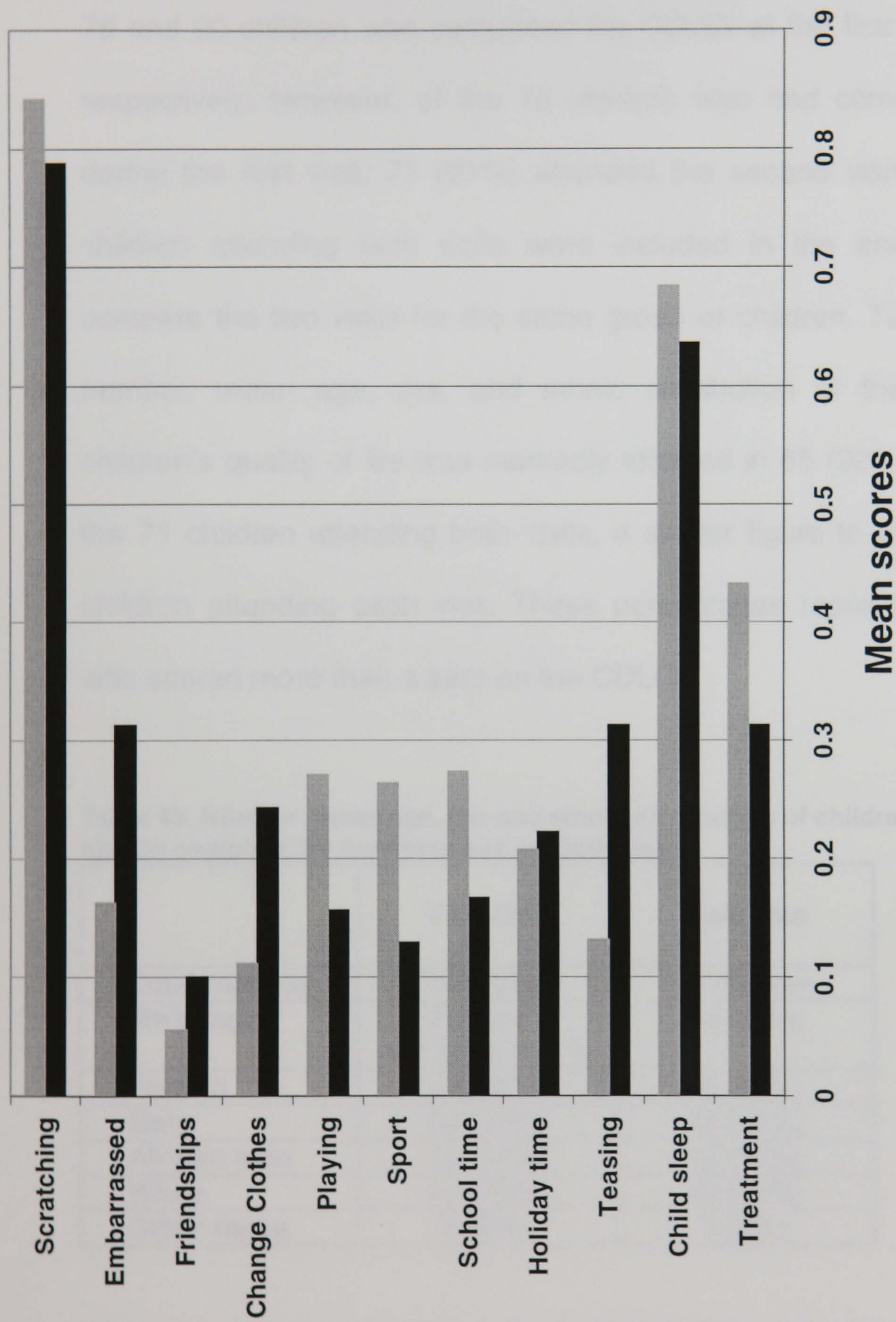


Figure 13. Mean scores of the CDLQI components for 71 males and females on the second visit

3.3.2.3 The total CDLQI on visits one and two

Children’s quality of life was affected in 72 (92%) and 71 (79%) children during the first and final visits respectively. The previous figures were for the 78 and 90 children who completed the CDLQI at the first and second visits respectively. However, of the 78 children who had completed the CDLQI during the first visit, 71 (91%) attended the second visit. Data for the 71 children attending both visits were included in the analysis in order to compare the two visits for the same group of children. Table 43 shows the number, mean age, sex, and ethnic distribution of these children. The children’s quality of life was markedly affected in 65 (92%) and 55 (77%) in the 71 children attending both visits, a similar figure to the total number of children attending each visit. These percentages represent those children who scored more than a zero on the CDLQI.

Table 43. Number, mean age, sex and ethnic distribution of children with AD who were able to complete the questionnaire on both visits

	Visit One	Visit Two
Total number	78 children	71 children
Mean age	8.6 years 8.5 years for 71	8.9 years
Female	44 (56%)	38 (54%)
Male	34 (44%)	33 (46%)
African skin	17 (22%)	13 (18%)
White	55 (70%)	52 (73%)
Other races	6 (8%)	6 (9%)

Of the 71 children attending both visits 38 (53%) showed an improvement, 12 (17%) remained unchanged, and (21) 30% showed an increase in the CDLQI scores. The initial mean of CDLQI for 71 children was 4.5 (SD 4.2), and 6 months later the final mean CDLQI was 3.2 (SD 3.7). representing a significant improvement perceived by the children (p= 0.007).

The CDLQI was significantly correlated with the SCORAD on the first and second visits ($r = 0.52, p < 0.001$) and ($r = 0.59, p < 0.001$) respectively. This remained significant even after controlling for potential confounders on visits one ($R = 0.13$; 95%CI, 0.05 to 0.2, $p = 0.002$) and two ($R = 0.18$; 95%CI, 0.08 to 0.3, $p = 0.001$). That is each unit increase in SCORAD had led to an average 0.15 unit increase in the CDLQI.

When the subjective scores were excluded from the SCORAD Index, the CDLQI remained significantly related to severity scores on the first and second visits ($r = 0.46, p < 0.001$) and ($r = 0.53, p < 0.001$) respectively. There was a direct positive correlation between the CDLQI and total SCORAD, which reflects the construct validity of the CDLQI. However, observer scores explained only 21% and 28% of the children's score at the first and second visits respectively.

Although the strength of eczema impact on the families and children was different, the CDLQI was significantly correlated to the DFI scores; $r = 0.37, p = 0.001$ and $r = 0.51, p < 0.001$ at visits one and two respectively. This means that parents and children evaluated the same problem with different attitude.

3.3.2.4 Changes in the CDLQI and disease severity over time

The mean change in CDLQI was -1.3 (SD: 3.8) with range of -13 to 10 and in SCORAD was -1.06 (SD: 10.7) with range of -30 to 33 . In multiple regression analysis, each unit change in SCORAD was associated with 0.12 (95%CI, 0.04 to 0.19, $p = 0.004$) units change in CDLQI. After adjusting for potential confounders (black skin, social class, sex, child's age, family size and region of residency), each unit change in SCORAD led to a 0.12 (95%CI, 0.04 to 0.2, $p = 0.003$) unit change in CDLQI. This finding shows the relationship between quality of life and disease severity over a 6 months

time. The differences in these two scoring systems are related despite the fact that the improvement in the CDLQI was statistically significant and minimal improvement in the SCORAD was insignificant.

3.3.2.5 Individual aspect of the CDLQI on visits one and two

Figures 14 and 15 show the percentage and mean scores for each aspect of children's life respectively for 71 children attending both visits. On visit one the highest mean score was in the question related to symptoms (itching) 1.17 and the lowest (0.19) was for friendships. These scores showed almost the same trend on the second visit.

3.3.2.5.1 Itchy “scratchy” or painful skin

Fifty-six (79%) and 46 (65%) children had an itchy “scratchy” or painful skin during the first and second visits respectively. This question had the highest impact on children's quality of life and also produced the highest over all mean score (see Figure 15). The initial mean score was 1.17 and after six months the mean final score was 0.82 representing a significant improvement perceived by the children ($p = 0.008$). Itching mean scores formed 23% and 25% of the total CDLQI scores during the first and second visits respectively (see Figures 16 and 17).

There was a highly significant direct but not linear relationship between itching scores and the observer's assessment of excoriation on visits one ($r = 0.36$, $p = 0.002$) and two ($r = 0.31$, $p = 0.008$). It happens that the value of r^2 (the square of the correlation coefficient – sometimes called the coefficient of determination) has a readily understandable interpretation in terms of the strength of a relationship between two variables (Daly and Bourke., 2000). Calculation of the coefficient of determination (r^2) was possible to evaluate

the effect of excoriation assessment on scratching scores. In the scratching and excoriation scores for example, r equals 0.36 and 0.31, so that r^2 equals 0.1296 and 0.0961 on the first and second visits respectively. Thus, the variation in the excoriation scores made by the observer explains only 13% and 10%, on visit one and two respectively, of the total variation in scratching scores by the child. The other 87% and 90% variation is unexplained and must be due to other factors not considered in this analysis.

There was also a highly significant direct but not linear relationship between itching scores and the observer's assessment of lichenification on visit one ($r = 0.37$, $p = 0.001$) and two ($r = 0.28$, $p = 0.019$). Calculation of the r^2 was possible in order to evaluate the effect of the assessment of lichenification on scratching scores. The r^2 was 0.1369 and 0.0784 for visits one and two respectively. Thus, the variation in the lichenification scores made by the observer explains only 14% and 8%, on visit one and two respectively, of the total variation in scratching scores by the child. The other 86% and 92% variation is unexplained and must be due to other factors not included in this analysis such as geographic area, social class, ability to cope with the disease and customs

3.3.2.5.2 Effect on child's sleep

Eczema had affected the child's sleep in 27 (39%) and 34 (48%) children on the first and second visits respectively (see Figure 14). This question had the second highest mean score (0.6 and 0.66 on the first and second visits respectively) after itching scores (see Figure 15). Scores on this question formed about 12% and 19% of the total CDLQI scores on the first and second visits respectively that constitutes the second major component of the CDLQI after itching (see Figures 16 and 17).

The effect on sleep was significantly correlated with the SCORAD-D ($r = 0.39$, $p = 0.001$) and ($r = 0.38$, $p = 0.001$) on the first and second visits respectively. By calculating the r^2 , variation in severity scores made by the observer explains only 15% and 14% on visits one and two respectively, of the total variation in sleep scores by the child. The other 85% and 86% variations are unexplained and must be due to other factors such as other illness, child's behaviour, not considered in this analysis.

3.3.2.5.3 Effect of treatment on the child

Twenty (31%) and 17 (25%) children were troubled by the treatment of their eczema at visits one and two respectively. However, the mean score for this question decreased from 0.43 to 0.38 representing a non-significant improvement recognised by the child ($p = 0.8$). There was a highly significant direct but not linear relationship between treatment scores and the observer's assessment of erythema on visits one ($r = 0.29$, $p = 0.021$) and two ($r = 0.35$, $p = 0.003$). When the r^2 was calculated to evaluate the strength of the effect of erythema assessment on treatment scores, it showed that the variation in the erythema scores by the observer explains only 8% and 12%, on visits one and two respectively, of the total variation in treatment scores by the child. The other 92% and 88% variation is unexplained and may be due to other factors such as personality and child's behaviour, not considered in this analysis.

3.3.2.5.4 Other components of the CDLQI

Twenty (30%) and 11 (16%) children were embarrassed or self conscious, upset or sad because of their AD during visits one and two respectively. The child being embarrassed or self-conscious, upset or sad because of her/his

skin, was significantly correlated to disease severity (SCORAD) on visits one ($r = 0.36$, $p = 0.003$) and two ($r = 0.37$, $p = 0.002$).

Atopic Dermatitis had affected a child's playing and doing hobbies in 20 (29%) and 11 (16%) children during the week before the first and second visits respectively. Childhood eczema had led to changing or wearing different or special clothes/shoes in 17 (29%) and 8 (12%) children during the week before the first and second visits respectively. While 18 (26%) and 7 (10%) children had avoided swimming or doing other sports during the week before the first and second visits respectively because of eczema. Eczema had troubled personal relationships in 12 (17%) and 13 (19%) children on first and second visits respectively. It also produced the lowest mean score 0.19 and 0.08 during the first and second visits respectively. No significant correlation with disease severity was found. And friendship was affected by AD in 10 (15%) and 4 (6%) children during the first and second visits respectively. Question about friendships had the lowest mean score 0.19 (SD 0.49) and 0.08 (SD 0.32) during the first and second visits respectively.

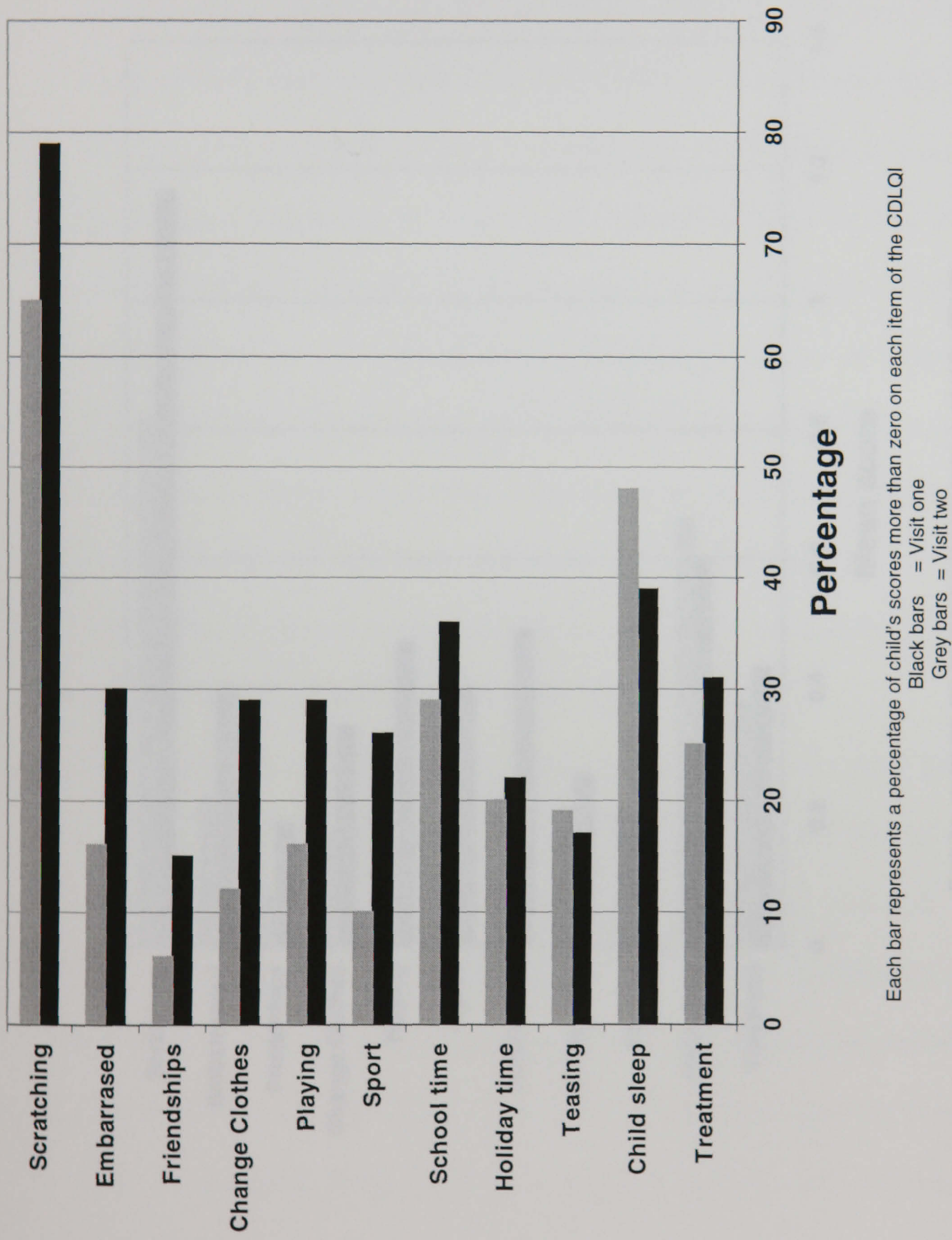


Figure 14. Percentage per aspect of child's life affected by their eczema for 71 children attending both visits

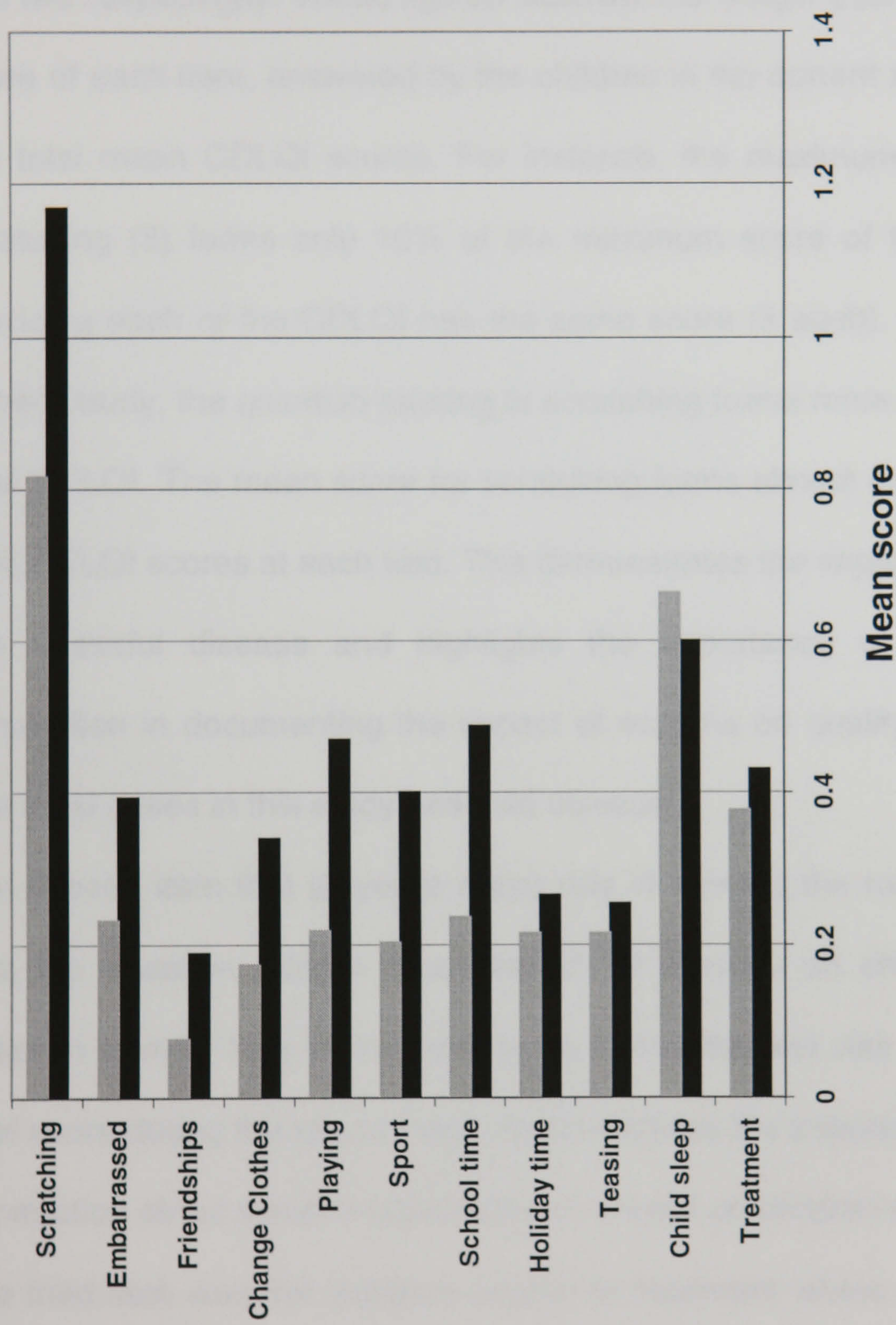


Figure 15. Mean score of each component of the CDLQI for 71 children attending both visits

3.3.2.6 Percentage “weight” of each item in forming the total CDLQI score

Figures 16 and 17 illustrate the percentage “weight” of the mean score of each item in forming the total CDLQI scores, in this population, on visits one and two respectively. These figures illustrate the weight exerted by the mean score of each item, answered by the children in the current study, in forming the total mean CDLQI scores. For instance, the maximum mean score of scratching (3) forms only 10% of the maximum score of the CDLQI (30), providing each of the CDLQI has the same score (3 each). However, in the current study, the question relating to scratching forms more than 10% of the total CDLQI. The mean score for scratching forms almost one quarter of the total CDLQI scores at each visit. This demonstrates the important of itching in this stressful disease and highlights the importance of including such information in documenting the impact of eczema on quality of life. Despite that most cases in this study had mild disease.

The second item that played a major role in forming the total CDLQI score was the question related to an impact of eczema on child’s sleep. The question formed 12% of the total score during the first visit and 19% of the total score during the second visit. Again it shows the importance of including information about sleep in quantifying an impact on children's quality of life.

The third item was the question related to treatment where it forms 9% and 11% of the total mean CDLQI score during the first and second visits respectively.

In this study with mostly mild cases, the mean score of the other 7 items in the CDLQI forms 56 % and 45% of the total mean CDLQI scores during the first and second visits respectively.

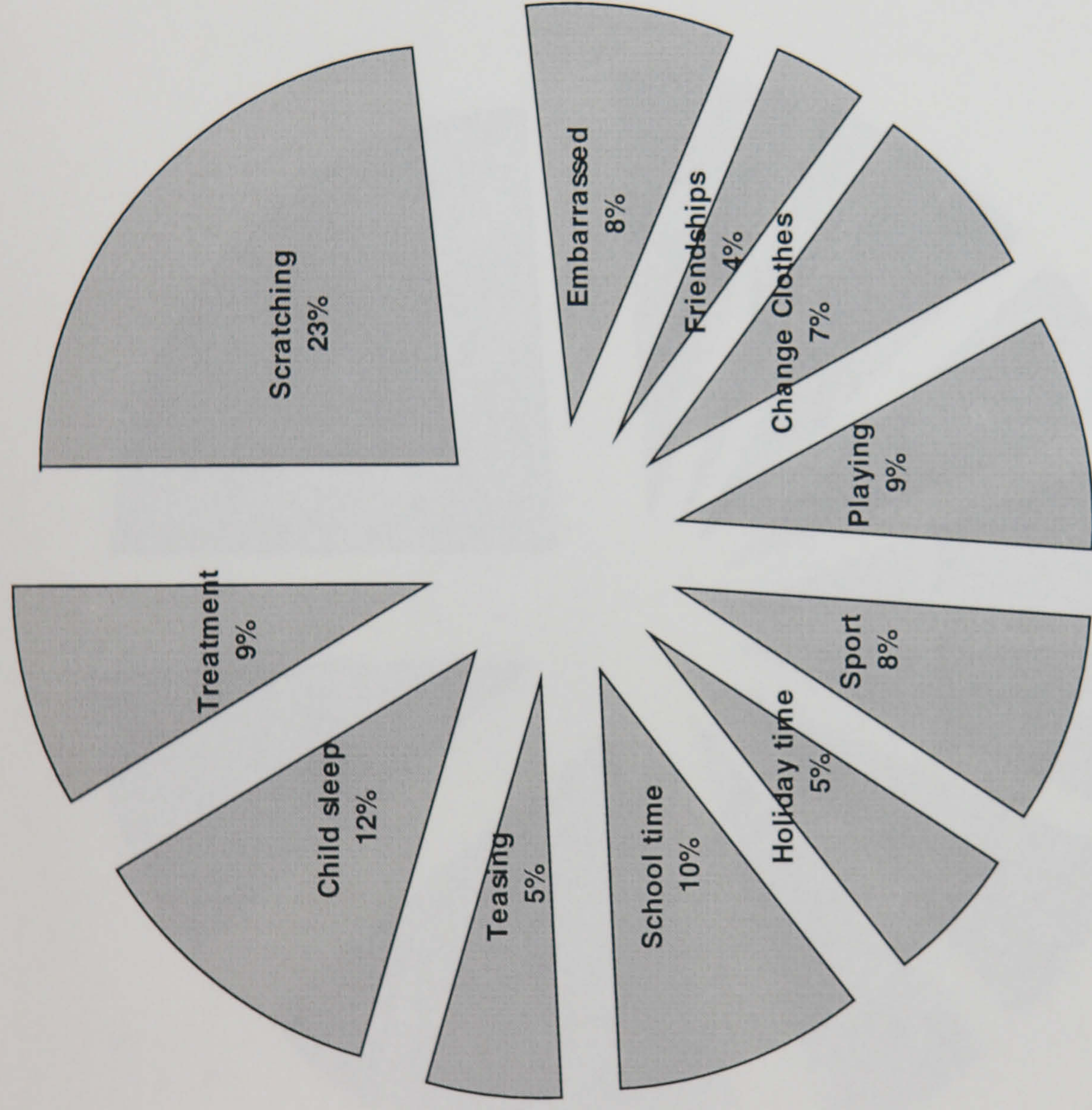


Figure 16. Percentage of the mean score of each item completed by the children in forming the total score of the CDLQI for 71 children attended the first visit

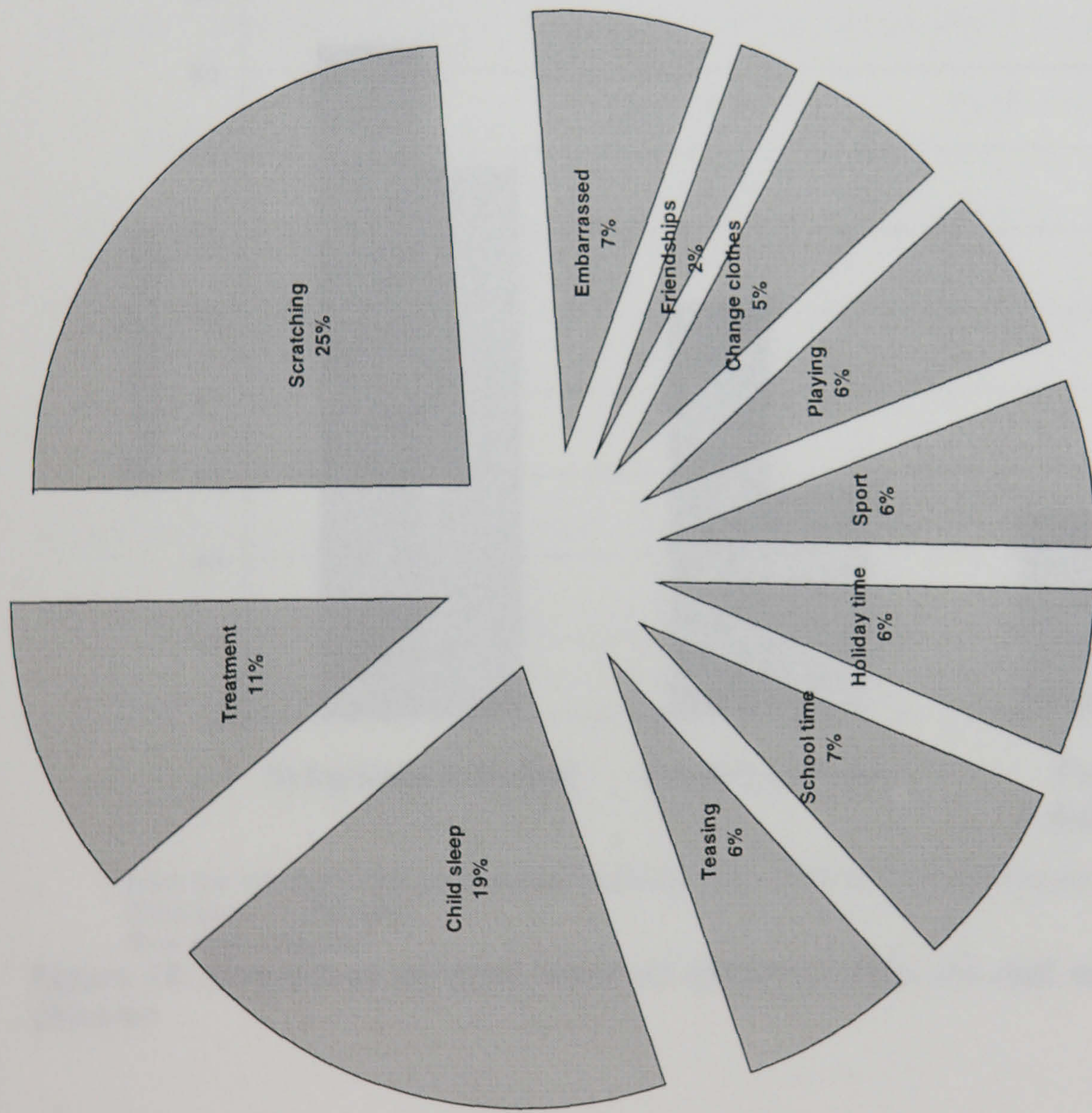
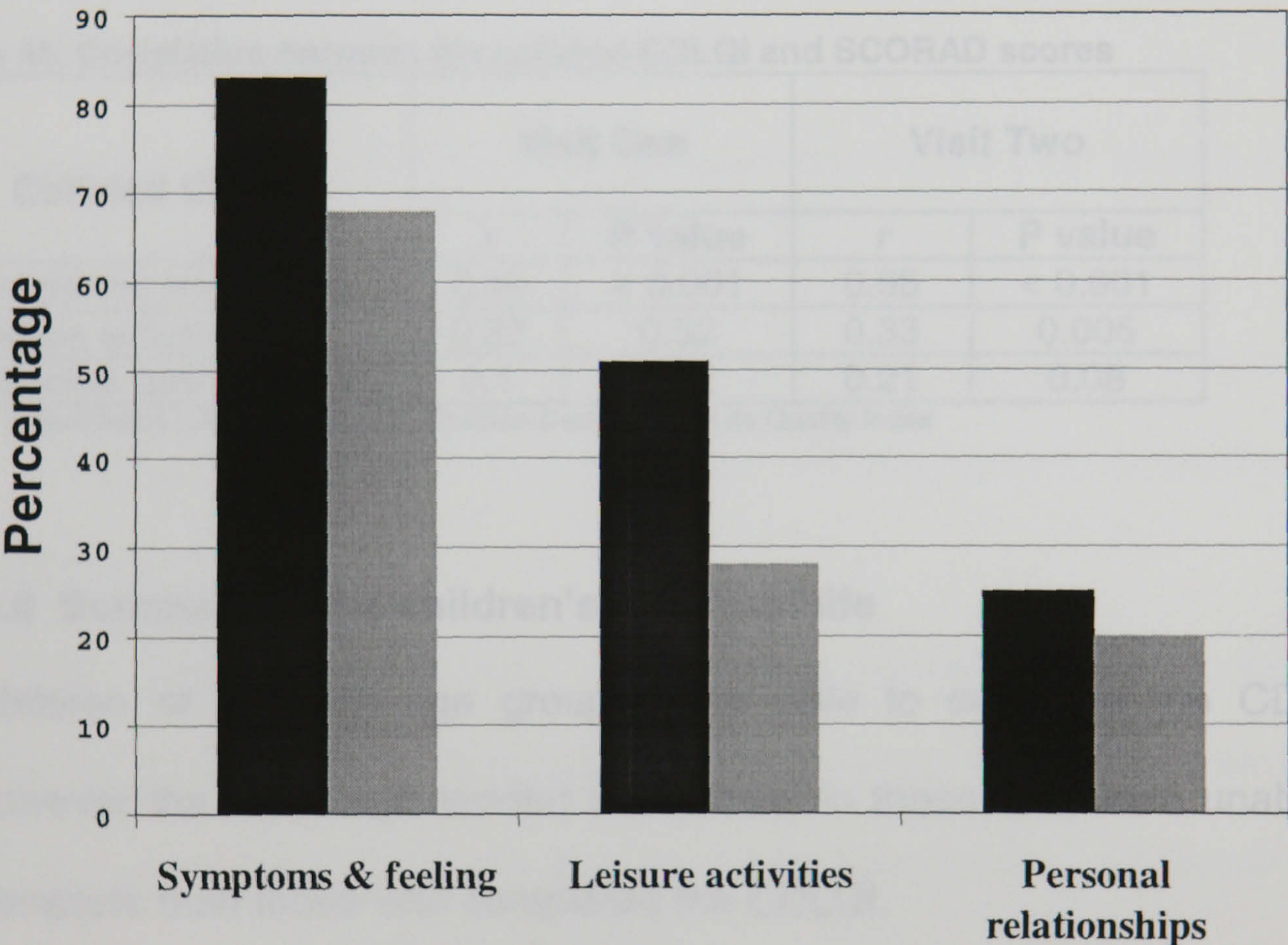


Figure 17. Percentage of the mean score of each item completed by the children in forming the total score of the CDLQI for 71 children attended the second visit

3.3.2.7 Collated scores of groupings of the questions at each visit

The impact of AD on three different aspects of QOL was analysed by grouping answers to those questions related to that particular aspect, i.e. symptoms and feeling (questions 1 & 2), leisure activities (questions 4, 5 & 6), and personal relationships (questions 3 & 8). On initial visit, symptoms and feeling were affected in 59 (83%) children and personal relationships were least affected in 25% of children only (Figure 18).



Each bar represents the percentage of that aspect of the child's life affected by eczema
Black bars = Visit one
Grey bars = Visit two

Figure 18. Percentage of three areas of children’s QOL on visit one and two for 71 children

The mean score of each aspect score is shown in Table 44, which was calculated using the “egen” command in the *Stata* software (Stata Corp, 1999).

Table 44. Mean (SD) of the collated CDLQI scores for 71 children

Collated CDLQI	Mean scores (SD) Visit One	Mean scores (SD) Visit Two
Symptoms and feeling	0.82 (0.69)	0.54 (.053)
Leisure activities	0.42 (0.59)	0.22 (0.52)
Personal relationships	0.23 (0.47)	0.22 (0.41)

Symptoms and feelings also scored the highest 0.82 (SD 0.69) and personal relationships scored the lowest 0.23 (SD 0.47). On the second visit, the same trend was observed. Symptoms and feeling had shown a significant positive and marginally strong correlation with disease severity measured by SCORAD on both visits. Personal relationships did not show any significant correlation with disease severity, while leisure activities showed inconsistent correlation, see Table 45.

Table 45. Correlation between the collated CDLQI and SCORAD scores

Collated CDLQI	Visit One		Visit Two	
	<i>r</i>	P value	<i>r</i>	P value
Symptoms and feeling	0.49	< 0.001	0.55	< 0.001
Leisure activities	0.23	0.52	0.33	0.005
Personal relationships	0.1	0.52	0.21	0.08

r, correlation coefficient. CDLQI; Children Dermatology Life Quality Index

3.3.2.8 Summary of the children’s quality of life

- Children of different age groups were able to complete the CDLQI, however the mean age tended to be lower in those who were unable to complete than those who completed the CDLQI.
- Most children aged 9 years or more were able to complete the CDLQI. This may imply that 9 years should be the lower age limit for using the CDLQI. The data suggested that all children with atopic dermatitis aged 9 years or more were able to complete the CDLQI without parents’ help, except one child who was unable to.
- Inability to complete the CDLQI was not significantly related to social class, ethnic background, or family size.
- Ninety-two per cent and 77% of children were affected by their atopic dermatitis on the first and second visits respectively. This highlights the

disability in children caused by eczema despite the fact that 80% of cases were graded as mild in severity.

- Disease severity had a positive and significant correlation with children's quality of life. This reflects the construct validity of the CDLQI, and may imply that the CDLQI can be used, within limited age groups, in a community-based study to evaluate the impact of eczema on children's life.
- There was an insignificant difference in the CDLQI scores as well as in its components between males and females.
- Male scores in the CDLQI have a stronger correlation than female scores with the SCORAD.
- In this study, children with atopic dermatitis provided information concerning their health-related QOL that was not typically available from their parents.
- Asking children directly and independently about their QOL has an important implication in obtaining information for patient management and evaluation of medical intervention in a paediatric setting. An experience that is both relevant and important to children with AD. Asking children directly about emotional burden, leisure activities, friendships, and treatment side effects can reveal this experience. Such information is valuable for a better understanding of atopic dermatitis burden and therefore to design a better intervention to reduce these burdens.

4 CHAPTER 4 DISCUSSION AND CONCLUSION

4.1 Section 1: General discussion

The study has revealed new findings in relation to the severity of childhood atopic dermatitis over time and the impact of this disease on children and the family's quality of life. It is the first time that eczema severity and impact on quality of life have been studied in a systematic way and in a community-based setting. The study has provided evidence that;

- Atopic dermatitis starting during the first year of life was a predictor of severe disease later on.
- Children with other atopic diseases (asthma and/or hay fever) have more severe disease than those who had no atopic diseases.
- Children with black skin who have AD are at higher risk of severe disease than their white counterparts and reliance on erythema scores can mask this disparity.
- Children with atopic dermatitis who live in an urban area were at higher risk of severe disease than their counterparts in a rural area.
- Family size, sex, birth weight, gestational age, child's age, parental atopy (hay fever, asthma, or eczema), and any atopy in siblings have no significant association with disease severity.
- Reaction to wool and some kinds of food was associated with severe disease, but their associations became statistically insignificant after adjusting for potential confounders.
- Social class and breastfeeding were not significantly associated with disease severity.
- Atopic dermatitis has affected both children and family's quality of life at different levels.

- Children's quality of life scores were significantly correlated to their atopic dermatitis severity as assessed by the observer.
- Family's quality of life scores were significantly related to eczema severity scores in their children as assessed by the observer.
- Changes in quality of life scores in both family and children were significantly related to changes in atopic dermatitis severity scores.

All these findings are important for a better understanding of atopic dermatitis. However, there are general points related to study design that should be discussed in this section before focussing on the main findings. These points are important for establishing the validity of this study's findings. For example any evidence of selection, information or measurement bias would make any conclusions drawn from this study debatable.

4.1.1 Study design

A longitudinal study design was implemented in this study to document the course of disease over a period of time because very little information about factors that may affect disease severity and the impact of AD on quality of life was available from a prospective design. Atopic dermatitis is a chronic relapsing disease and its course may vary over time. The longitudinal design enabled the documentation of disease severity over time and also factors that affect severity over time. The design allowed documentation of the impact of disease that comprised mostly mild atopic dermatitis, on children and family's quality of life at a single point in time and over a period of time. Because of this design, it was also possible to show that changes in quality of life scores were related to changes in severity scores. However, longitudinal studies may suffer from a high drop out rate due to different

reasons. If the rate is high, subjects may have a substantial difference in the main outcome. Fortunately, this study had a low drop out rate (12%) and this would make any potential substantial difference in these subjects from those attended the last follow up less likely to have a significant effect on the outcome.

A retrospective study design is easy to carry out and is less expensive, but it is associated with problems in the collection of data from patients' notes. Another disadvantage is that it is not possible to assess disease severity in a systematic way. A study with a cross-sectional design provides information regarding the effect of factors at one point in time and not over time. In a chronic relapsing disease such as AD, exploring factors that may affect disease severity over time is more important than exploring their effect at just a single point in time. Therefore the longitudinal design implemented in this study was ideal for investigating factors that may affect disease severity over time and the impact of AD on quality of life.

4.1.2 Bias

4.1.2.1 Selection bias

The most crucial problem in carrying out this epidemiological study was to select appropriate subjects representing the targeted population; thus a representative sample of children with AD was needed. It is important to consider whether there was a selection bias due to the selection of GP's in this sample. This is a community study and general practices were not selected randomly, even though they were representative of the general practices in both areas studied. Generally, subjects, whether they have disease or not, register with the nearest GP group in the area, and there is no

evidence to suggest that patients with eczema have a tendency to register with one GP rather than another.

Another point of concern was the low response rate, which was generally low, in particular from the urban area (35%). For example, practice number two, in the urban area, had the lowest response rate (26%). One explanation might be the way the GP had coded the cases of AD, which had led to confusion with other diseases. This speculation was supported by data from this study in which 3% of parents who responded had moved from the area and another 6% denied that their children had ever had eczema.

On the other hand, practice number seven from the rural area had the highest response rate (100%). The GP in this practice said “They were the only cases with atopic dermatitis registered with our practice in this age group. All of them were happy to help and, in fact, other parents were upset that their children were not included (from a different age group) in the study”.

One explanation is that in a very small community where everybody knows everybody, the relationship between doctor and patient is often closer.

Another reason that could be a potential source of bias is that the GP in this practice has a special interest in dermatology and is a leading member of the Primary Care Dermatology Group. These two practices represent two ends of the spectrum in this study. This queries the way in which GPs had chosen the list and may explain the low response rate in some situations. Another explanation is that GPs may have included many cases with very mild eczema, which can be treated by an emollient or patients with just dry skin.

Therefore parents might have thought that these cases were not of any help.

This speculation is supported by the fact that some GPs did use repeat prescriptions for emollient to create the list of potential patients. It was

impossible to investigate the latter speculation because access to patients' notes was not part of the study protocol.

In general, the response rate per individual practice was quite low in the urban area compared with the rural area. This raises three questions: First, are patients from the urban area less motivated to participate in such studies? Second, was there any bias in the way that GPs had created the list of potential patients? Thirdly, if one GP is more interested in dermatology research than another does this have an effect on recruitment? Unfortunately it is not possible to answer these questions directly; although the design is supported by indirect evidence when the children with visible eczema only were ranked into three categories. The severity distribution of this population was the same as in other studies (Dotterud, Kvammen, Lund, Falk., 1995; Berth-Jones *et al.*, 1997; Emerson, *et al.*, 1998). All this information suggests that there was no intrinsic bias towards disease of low severity and therefore selection bias, due to GPs preference, is less likely to have occurred.

A potential way to rule out selection bias in cases of low response rate is to contact the non-respondents and investigate if their disease state was substantially different to those who responded. Unfortunately, it was generally impossible to contact the non-responders. Even if it had been possible, it would have required an examination and assessment of their eczema severity and documenting the ratio of the impact on their quality of life in order to rule out any substantial differences. As they had shown no interest in the study at all, it was deemed unacceptable on ethical grounds to proceed further.

Another potential source of selection bias was the way subjects themselves participated. The responders who had volunteered to help could have been

either healthier (no disease) or sicker (having severe disease). The total low response rate could have led to selection of a certain group of patients with specific characters. However, it is believed that this form of selection bias is less likely for the following reasons;

1. When the SCORAD-D was ranked into three categories (mild, moderate, and severe), the severity distribution of this population had approximately the same severity distribution as in Nottingham, UK, the study with a higher response rate (84%) than this study (Emerson, *et al.*, 1998). Another community study in Leicester with high response rate (83%) compared with this study found that 82% of children had mild eczema (Berth-Jones, *et al.*, 1997). This suggests that there was no intrinsic bias to disease of low severity and no overrepresentation of mild cases.
2. When children's QOL was the outcome of interest, the mean scores of the CDLQI at each visit were similar to the mean scores found in other community-based studies (Emerson, Williams, Allen, *et al.*, 1997; Lewis-Jones, *et al.*, 1998). The mean score in Emerson's study (1997) was 3.8 (SD 4.2) using an instrument designed to measure the impact of any disease on children (This questionnaire has not been published yet). In Lewis-Jones' study (1998) the mean score of the CDLQI was 2.93 (Lewis-Jones and Finlay., 1995). Both of these studies, by Emerson *et al* (1997) and Lewis-Jones *et al* (1998), were published in abstract form and have different study designs. A further critical approach to these studies was not feasible because of the limited data provided in the abstract. However, it suggests that intrinsic bias to children with a low impact on quality of life is unlikely.

3. When the family's quality of life was the outcome of interest, the mean scores of DFI at each visit were similar to the reported DFI scores from a study in rural practice (Lewis-Jones, *et al.*, 1998). This suggests that intrinsic bias towards parents, for whom there was a low impact on quality of life, was unlikely to have occurred.
4. Other exposure factors such as age of onset and ethnic group have similar distributions to those seen in other studies (Balarajan and Raleigh., 1992; Queille-Roussel, Raynaud, Saurat., 1985).

It is maintained, therefore, that the cases in this study are representative, although an overall underestimation cannot be excluded completely. Finally, this is a longitudinal study with a relatively good total follow-up rate (88%) and there was no substantial difference in disease severity between those who dropped out and those who continued in the study. In addition an 88% follow rate would make any substantial difference between those who attended the last follow up and those who drop out, less likely to affect the outcome.

4.1.2.2 Information bias

It is clear in this study, as well as in any other studies that rely on maternal reporting of events, that the problems of definition and recall could not be entirely avoided. The clinician in a paediatric population depends completely on the history taken from the parents. In this study however, information about risk factors was gathered by a piloted and structured questionnaire that depended, in most questions, on recall from the last 6 to 12 months. Few questions had a longer recall time such as age at onset, breast-feeding, birth weight, and severity at onset. The piloted and structured questionnaire would have made information bias less likely to occur and any potential source of

information bias regarding exposure will be discussed specifically in relation to that particular factor.

4.1.2.3 Measurement bias

It was impossible to make the observer blind to some exposures (area of residence, sex and skin colour) in this population. He was the only observer who assessed disease severity all the time. However, during the study the observer did not know the results of the questionnaires (exposure) and was completely blind to these exposures, except area of residence, sex and skin colour. This is an inevitable drawback of this study regarding these factors and carried a potential risk of bias. To investigate the effect of measurement bias on this study finding, a parental score on a 0 to 10 analogue scale was used. To avoid repetition when discussing these factors (ethnic background, sex, or area of residence), it should be emphasised here that the finding remained the same, whether it was significant or insignificant, when the parents' scores were used in their own. Also, when quality of life was the outcome of interest the observer remained blind to the questionnaire (the DFI and CDLQI) results.

During assessment of severity the dependence on a single observer may have removed the inter-observer variability but left the study with intra-observer variability, a feature that could not be avoided. Hence observer bias cannot be totally excluded. This may take the form of detection bias and can be partially eliminated by double-blind controlled trials in an experimental design, but in epidemiology it is nearly impossible to eliminate. One should always be open to consider alternative explanations (bias and/or confounding effect) when interpreting results because randomisation and blinding is usually impossible in population studies.

4.1.3 Inclusion criteria

Comparison is at the heart of clinical epidemiology and subjects compared should have similar behaviour. The UK diagnostic criteria for AD were used to ensure that subjects included had the same disease (Williams, *et al.*, 1994a, 1994b, and 1994c). There is only one sign (flexural dermatitis) in these criteria, which was documented by a previously trained observer according to the guidelines suggested by Williams and others (1995b). All these were implemented to select patients in the same entity. The criteria have a sensitivity of 80% and a specificity of 97% when validated in a community study (Williams, *et al.*, 1996) but it is possible to speculate that there will be atopic dermatitis cases that do not fulfil the criteria. Unfortunately the study demonstrated this obstacle in that 14 (10%) children whom the investigator felt had or had had AD, but they did not fulfil the UK diagnostic criteria. An ideal way to deal with this problem is to carry out the analysis for each factor, with and without inclusion of these children. This would have been both complicated and impractical to implement and possibly confusing to the reader. Simple exclusion would have had the potential to introduce bias in the study as these subjects potentially might relapse and then fulfil the criteria. Against exclusion therefore are the following points;

1. Some of these children had flexural postinflammatory hyperpigmentation, which indicated previously active eczema – but only if they were to relapse would they fulfil the criteria.
2. A survey of childhood atopic dermatitis in London found that only about half of children with a history of this condition had identifiable dermatitis during the survey (Williams, Pembroke, Forsdyke, *et al.*, 1995a). There was similar finding in the current study where 54% had visible flexural

dermatitis at recruitment. Williams' and this study's findings suggest that atopic dermatitis has a relapsing nature and it is possible that this would underestimate the prevalence if one was to rely on visible dermatitis only. In these two studies about half of the patients did not have visible eczema.

3. Eleven (79%) children of the 14 had one major and two minor criteria. For instance if they were to develop asthma and/or hay fever and they would then satisfy the criteria. Asthma and hay fever are unstable diseases with unpredictable prevalence, yet atopic dermatitis patients have a higher risk of developing both (Gustafsson, Sjoberg, Foucard., 2000). The longitudinal design of this study allows the previous possibility to occur and the absence of any predictive information on the disease outcome (Williams and Strachan., 1998) would make excluding them unjustifiable.

However, when the sensitivity analysis was carried out before and after excluding these 14 patients, the outcome was the same, and it was therefore deemed justifiable to include them. It also should be emphasised here that this inclusion was not to increase the number of observations and therefore the statistical power. It was carried out to make sure that all subjects with the same disease were included.

4.1.4 Disease severity assessment

4.1.4.1 The SCORAD index

The SCORAD Index was developed to assess disease severity in a standard way (European Task Force on Atopic Dermatitis., 1993). A recent review by Charman and Williams (2000b) concluded that the SCORAD was the most tested instrument but there was significant inter-observer variability. The latter had no effect on the results of this study because only one observer assessed disease severity all the time. This would therefore add strength to the study result and misclassification seems unlikely to have influenced the results. Nevertheless intra-observer variability cannot totally be excluded in this study as it often occurs in epidemiological studies.

Another weakness of the SCORAD index was the usage of the rule of nines to assess disease extent. It has been reported to have very poor inter-observer agreement when it was used to assess disease extent in 6 patients with AD, and also showed low intra-observer variation with perfect agreement, in only 4 of 6 cases (Charman, Venn, Williams., 1999). However in this study, the same observer assessed disease extent all the time, which should satisfy the suggestion made by Charman *et al* (1999) in which a single observer should be used. Memory recall bias could not have happened because subjects were re-examined after 6 months that was long enough for the previous assessment to bias the next. The observer in this study also was previously trained while in Charman's study (1999) the investigators were not trained before hand. In the absence of objective markers for disease severity, using the rule of nines, even with it's limitation, still provides systematic information about disease extent. Therefore

substantial effects were unlikely to occur because subjects had nearly the same severity distribution as in other studies (Berth-Jones, *et al.*, 1997; Emerson, *et al.*, 1998).

A comprehensive severity instrument should measure signs and symptoms. The first of these reflect the physician's assessment of any visible sign and the second reflects patient's assessment of their disease. Although symptom assessment is more subjective, it should be included because it evaluates an outcome of the visible sign, as perceived by the patient. Combining subjective and objective assessments could be a source of bias in disease severity assessment because there are at least two different observers involved in this process. However, it is also the only way of obtaining a comprehensive view of the disease status. For example in atopic dermatitis, itching and sleep loss, probably in most cases, are the immediate outcomes of disease and a cause of major concern to the patient (Lewis-Jones and Finlay., 1995). Itching and sleep loss can be encountered even in the absence of visible eczema. Any scoring system that does not include them would not provide a comprehensive view of disease status.

The observational design of the study did not permit any interference with the patients' activities including self-medication. Ideally in order to score dryness the parents would have been told not to apply emollient before clinical examination. Therefore the dryness score was excluded from the SCORAD. This may have affected the internal consistency of the SCORAD index and therefore could be a source of bias. However, it has been documented that the SCORAD remains a valid instrument of severity assessment even after exclusion of dryness and subjective symptoms when a group used

photographs to train 98 investigators from different disciplines (Oranje, Stalder, Taïeb, *et al.*, 1997).

Another inadequate validation of the objective scores was the positive and significant correlation to the global severity assessment by the parent on a 0 to 10 scale. Although the former is rather weak validation of the observer scores, it seems a reasonable approach in the absence of any 'gold' standard marker for atopic dermatitis severity. Thus exclusion of dryness is unlikely to have underestimated the disease severity in this population.

4.1.4.2 Practical meaning of the units used in the SCORAD

It is well known that a subject with blood pressure of 190/150 has hypertension, as it is clear from this study and other studies that a patient with SCORAD of 60 or more definitely has severe disease. But what does a one unit or 10 units increase in the SCORAD mean clinically? If one could explain what a one unit increase in the SCORAD means clinically, one also could explain what a one-millimetre increase in assessment of blood pressure by a sphygmomanometer means clinically, a more objective scale used to assess blood pressure. These two techniques represent two ends of the spectrum, the sphygmomanometer with its objectivity validated using physics produces an objective gold standard, but the SCORAD with less objectivity measures a disease state for which there is no pre-existing gold standard. However, these two techniques (Sphygmomanometer and SCORAD) are used to assess an outcome in a systematic and repeatable way. So what really matters, at the current level of knowledge of the subject, is the validity, reliability and applicability of the technique. It has been reported that the SCORAD, used in the current study, proved to be the most tested technique for validity and reliability (Charman C, Williams., 2000b).

What a one or 10 unit increase in the SCORAD means to the patient is a task that has not been achieved yet. Scoring atopic dermatitis is still in its early days and may be improved by time.

4.1.4.3 Suggestions that may improve the SCORAD

The SCORAD was an easy instrument to use in the assessment of AD severity in this study, and it is recommended for usage in other observational studies. Nevertheless, it is possible to suggest a few points that may improve the SCORAD, bearing in mind that designing a new instrument was outside the original goal of this study.

1. Using the rule of nines in the SCORAD. It would be easy to divide the body areas into several areas similar to those used in the NESS (Emerson, *et al.*, 2000) because of the difficulty in precisely marking the end of the lesion. This may improve the accuracy and decrease the time needed to score the disease severity in a patient.
2. Usage of the SCORAD in an observational study necessitated exclusion of the dryness score from the total SCORAD. In this study, the exclusion of dryness did not affect the SCORAD and therefore it is possible to use this scale without this sign.
3. SCORAD users should be aware of the difficulties in scoring erythema in pigmented skin and treat its score as a confounder and control for it in the analysis. An alternative suggestion would be to exclude the erythema score from the SCORAD index. But it should be emphasised here that using hyperpigmentation instead of erythema is not good alternative.
4. The SCORAD is a point measure of disease severity and does not reflect the disease status in the time prior to that point. Theoretically

one may suggest that assessment of disease severity everyday and taking the average score may give an average of disease activities over this time of measurements, but there are practical constraints. Even if it was possible to find cooperative subjects, the variation in the observer assessments and the fluctuation in the disease course on a day to day basis inevitably make these more complicated. On the basis of practicality, the SOCRAD cannot truly be used in this way. Also the effect of each measurement on the subsequent one may be significant because 24 hours is a short time and this may bias the next measurement, if the same observer is used.

This study got around this by taking average disease activities over a period of two years. However at this point, it is not possible to provide an objective way of measuring disease fluctuation over a short period. One might suggest a subjective measurement of disease fluctuation by asking the subject about number of flares in the last week, month or even longer, bearing in mind that the longer the recall time, the less the precision of the answers. However, asking the subject would decrease the objectivity and increase the subjectivity. The issue of disease fluctuation in this study is dealt with later in the discussion on AD course, and in the current state of knowledge of AD it is not possible to assess 'average' activities of AD objectively without asking the subject.

In summary, the SCORAD proved to be an easy and valid technique to assess AD severity in the current knowledge of the disease. However, the suggestions made may improve its validity and practicality.

4.1.5 Quality of life assessment

The design of some general health quality of life instruments may underestimate the magnitude of the problems caused by skin diseases. In this study two different (speciality and disease specific) instruments were used to quantify the impact of atopic dermatitis in children on themselves and their families' quality of life. The DFI was used to assess families' quality of life without any restriction and in accordance with the guidelines suggested by the authors (Lawson, *et al*, 1998).

The CDLQI, however, was used with some slight restriction. The impact on the parents was quantified by the DFI. Thus, asking parents to help in completing the CDLQI would have provided information on the impact on parents and not on the children, a variable that already has been measured. It was therefore decided to prevent parents from helping with completion of the CDLQI, a restriction that might make one question the validity of the CDLQI as used here because the parents, according to the instrument design, were allowed to help children to complete the CDLQI (Lewis-Jones and Finlay., 1995). While this concern is understandable the method used was the only way that the impact of eczema on children's quality of life, without parental influence, could be quantified in the absence of any other reliable and valid instrument. However, there are two findings, from this study, that lend support to the validity of using the CDLQI in this way. First, the significant positive correlation between quality of life and disease severity established the construct validity of the CDLQI in this group. Second, 98% of children aged 9 years or more were able to complete the CDLQI, when only 50% of children aged 8 years or less were able to complete the CDLQI. This finding suggests that older children can complete the questionnaire without

parental help, which perhaps reflects the fact that the CDLQI can be used in this age group. The first finding showed the construct validity and the second showed the applicability of the CDLQI and taken together these confirm that the CDLQI is still a valid instrument for quantifying QOL in children with AD and the restriction implemented did not affect the outcome.

4.1.5.1 Lessons learned from using the DFI

It should be emphasised here that it is neither the aim of study to validate the quality of life scale nor to develop a new scale to measure quality of life in atopic dermatitis. But what was important was the justification of using these scales in this study. Design and validation of a new scale requires a different study design that would allow examining the validity, reliability and applicability of the scale. However, there are some points to suggest that should be taken in consideration when designing or using such scale.

The DFI was easy to use in this study, which was reflected by the high percentage of parents who were able to complete it. Therefore, the DFI was easy to use. On the other hand the DFI was positively correlated with the children's AD severity, which reflects its construct validity. And finally the crude validity was shown by the ability of the DFI to give higher scores for visible than non-visible eczema on the same site.

However, it was not possible to speculate or test what a one unit increase in the DFI means to the parents in practical terms. Quality of life assessment in dermatology is still in its early days and in the current state of knowledge, it is not possible to assume that a DFI score of 20 means that parents were affected twice as much as parents who scored 10 on the DFI. It was possible to show that a 10 unit increase in the SCORAD was associated with a 3.8

unit increase in the DFI, but what was not possible was to give any biological meaning for each unit increase in the DFI.

One suggestion one may add by increasing the recall time from one week to an average last 12 months. However, this may affect the precision of the information.

4.1.5.2 Lessons learned from using the CDLQI

The CDLQI was designed to quantify the impact of any skin disease on the QOL (Lewis-Jones and Finlay., 1995). Apart from the reading ability that improved as the children get older, the CDLQI was an easy instrument to use for assessing the impact of eczema on children quality of life. The positive correlation between the CDLQI and disease severity demonstrated its construct validity. The questionnaire focuses on items of special concern to the children with skin disease such as itching and sleep loss that are conceptually less demanding and therefore more valid. However there are a few suggestions that may improve the CDLQI in the future:

1. Increasing the recall time might give an average impact on the last year for example although this might lead to decrease in data precision.
2. The CDLQI completion by young children might be improved by change the wording of the questionnaire. It is a hypothetical suggestion based on assumption that those who did not complete the CDLQI were unable to understand the questions. It should be stressed here it is assumed that the CDLQI is going to be used without any help from anybody including parents.

3. Question 7 can be made easy to read by dividing it into A and B. Also its current position might be confusing. To keep the same style question number 7 could be moved to be the last question.
4. The completion might be improved by asking the observer to read the questionnaire and explain it to the children (face-to-face interviews). This would avoid the parents' input but the child might be embarrassed and then would not give a precise answer.
5. In this study, answers to question numbers 1, 9 and 10 accounted for nearly half the CDLQI scores. This may make one speculate about changing scores given for each item in the CDLQI so that 1, 9 and 10 would have 15 units out of the 30, the rest being shared between the remaining questions. This would provide a greater degree of differentiation based on the present study. But this study population comprised subjects with AD only where, itching and sleep loss were the most important symptoms. However, this may lead to underestimation of the impact of non-itchy skin conditions such as acne, warts as the CDLQI was designed to measure the impact of any skin disease on quality of life and not only eczema.

Nevertheless, the CDLQI appeared to be practical, valid and easy to use in children aged 9 years or more.

4.2 Section 2: Atopic Dermatitis Severity

4.2.1 Course of AD

4.2.1.1 Severity of eczema when first started

Parents gave higher scores for their children's eczema severity when it first started than the scores given at the final visit in the study. This means that eczema severity had improved in parallel with an increase in the child's age, according to the parents' evaluation. They rated disease severity when it first started, but this involved varying recall times. This could be a source of bias because the assessment was documented at the time of recruitment in respect of something that had happened some years previously.

Also, the presence of visible eczema on recruitment may have affected the reliability of this assessment and therefore could be a source of bias (Kulig, Bergman, Edenharter, Whan, and the Multicenter Allergy Study Group., 2000). However, the child's eczema had improved from when it first started according to parental evaluation, which was demonstrated by a highly significant decrease in mean severity scores. Although this was a subjective assessment, it represented a highly significant improvement from the parents' point of view from the time of disease onset to the day of the final visit. These findings supported the previously reported improvement of AD with age (Williams and Strachan., 1998), despite the limitations of both studies (William's and the current study). This is an important finding but note should be made of the subjectivity of severity assessment by parents and the potential information bias.

4.2.1.2 Best season in the year for eczema

With 38% of children parents felt that summer was the best season for their children's eczema. This may indicate a subtype of eczema that gets better during a warm environment. Hot weather, no central heating and exposure to more ultra violet light might also explain eczema improvement during this season. The effect of other factors such as holiday time and exposure to other aeroallergens cannot be excluded from the available data.

4.2.1.3 Topical steroids

The study showed that 90% of parents were applying or had applied steroid cream or ointment to the child's skin. Although the question about topical steroids (creams/ointment) was straightforward, the unlimited recall time might have affected the reliability of this question (see question number 33 in Appendix 6.2 and question number 20 in Appendix 6.3). Also, it may have been interpreted as including the usage of topical treatment in general, i.e. for other conditions. However, when parents were asked about the frequency of steroid application in the last 6 months preceding the final visit, 63% of parents had applied topical steroids at different frequencies (i.e. less frequent, every other day, once a day, or twice a day). The pattern of answers was therefore consistent as all the parents answered exactly the same question with a 6 months recall time. Another observation that supports the construct validity of the question, about topical steroid frequency, was that observer assessment of eczema severity had increased with an increased in the frequency of topical steroid application. There is also evidence that support the internal consistency of the questionnaire where parents were able to give high scores in accordance with more frequent application of topical steroid.

Although the term 'steroid cream/ointment' used in this study's question about topical steroid usage was similar to the term used by Charman *et al* (2000a), the outcome of these two studies was different. In this study the information gathered was about the usage and frequency, but in Charman's study (2000a) the outcome was worry about using steroids. This explains why in the latter study 72.5% of those asked were worried about using topical steroids while in this study parents of 37% of children did not apply steroid in the last 6 months.

Although there was a significant statistical difference in disease severity between those who applied topical steroids and those who did not, this finding was not considered for further analysis. It is more likely that patients with severe disease were more likely to use topical steroids and not that usage of topical steroids had lead to severe disease. This finding represent a result that is statistically significant but not necessary clinically relevant. Researchers should be aware of such finding. Allergy to any of the cream/ointment components, though, cannot be ruled out in the current study design.

The main reason for including questions about topical steroids was to document the usage and to check the internal consistency of the questionnaire. It also helped to validate the observer's scores, which had shown a trend to an increase in the severity score for question 20 (Appendix 6.3) with an increased frequency of topical steroid use, except for the once a day category which is probably due to the low number of subjects in that group.

4.2.1.4 Admission to hospital

Less than 2% of children had been admitted to hospital, which reflects the fact that most cases were mild and did not warrant hospital treatment. Again this finding adds strength to the study results and makes selection bias less likely and in agreement with the finding of Emerson and colleagues that the majority of AD cases were managed in primary care (Emerson, *et al.*, 1998).

4.2.1.5 Systemic treatment

This study showed that less than 4% of children had used systemic steroids, an expected finding in a community-based study where most of patients have mild disease. It indicates that the majority of cases in this study were mild, a finding that has been documented in other studies (Berth-Jones, *et al.*, 1997; Emerson, *et al.*, 1998). Oral antibiotics were used more frequently than oral steroids. The range of those receiving oral antibiotics varied from 50% before the first visit to 17% before the fourth visit. The latter is more reliable as all parents answered exactly the same question while during the first three visits answering the same question involved different recall times. The same applied to other systemic treatments.

When disease severity from the fourth (final) visit was examined, the observer was able to give higher severity scores for those who used antibiotics and prednisolone than who did not. Both drugs tend to be used in infectious and severe eczema. The observer could not be biased by the exposure because the information about the latter was only revealed after the study had finished. Therefore the SCORAD used by the observer to assess AD severity, was able to detect (although not statistically tested) higher scores for those with, presumably, more severe disease.

Oral antihistamines were taken in the last 6 months preceding the final visit in 19% of children. The mean SCORAD-D was similar in those who used and did not use oral antihistamines. However, the mean subjective symptoms' scores were higher in children who received oral antihistamine than those who did not. This may indicate that itching and/or sleep loss were encountered even when the eczema got better.

4.2.1.6 Atopic dermatitis severity fluctuation over time

Atopic dermatitis is a chronic relapsing disease with an unpredictable course over time. Information on short-to-medium term fluctuation and factors that may affect this is scanty (Williams and Wuthrich., 2000b), information that is needed for everyday practice and evaluating any new treatments. In this study, it was clear from the observer assessment that signs did fluctuate over time. However, the problem was to find a marker or a surrogate that could represent quantification for instability in disease severity. Theoretically standard deviation (SD) of the objective scores (SCORAD-D) could be used as a surrogate to represent severity fluctuation. But at each time point SD may also reflect intrinsic "inaccuracy" of measurement by the observer, even, if there was no change in disease severity at all. Therefore, it was decided that SD would be an inappropriate surrogate to assess severity fluctuation. The 6 months period between each visit may also not be ideal for the assessment of severity fluctuations.

Objective and systematic evaluation of severity fluctuation remains a difficult task. However, history of disease duration or frequency of exacerbation in the last 6 months before clinical assessment may provide information about the severity fluctuation, but this still remains subjective, as a different observer would assess disease severity. This therefore might underestimate or

overestimate the actual disease course. It, therefore, was not possible to investigate those factors that may affect severity fluctuations.

4.2.2 Severity over time as the outcome

The summary measures and statistical analysis used in the current study had calculated the odd ratio for severe disease using 'average' disease activities over a period of time per subject and not at a single point in time. By using this approach it was possible to get around the problem of the SCORAD being a point measurement. Nevertheless, an individual remained the unit of analysis despite using the total number of observations from the four visits.

4.2.2.1 Intrinsic factors

4.2.2.1.1 Age at onset

Eczema starting during the first year of life was a predictor of severe disease later in life. This holds true after adjusting for important potential confounders such as location of residence and the presence of atopic diseases, although these proved to have a significant association with disease severity. The exposure status regarding the age of onset in this study was not biased and was consistent with other data found in the literature in which most cases were found to occur during the first year of life (Schmied and Saurat., 1991). From another study with a similar distribution of disease onset, the majority starting during the first year of life, Queille-Roussel, *et al* (1985) reported no association between age of onset and disease severity. The latter study recruited subjects from both in and out-patient populations of a specialised paediatric dermatology unit and the investigator used a locally constructed system to assess disease severity. The dissimilarity in study design and severity assessment may explain the contrasting findings.

Eczema in the mother may be considered as a potential confounder; so is it appropriate to adjust for the mother's eczema? A mother with experience of eczema may recognise the disease sooner in her child than a mother without such experience and so cause it to be diagnosed earlier. She may also give a higher score to the same symptoms because she can imagine more easily what her child may be suffering. So eczema in the mother could be a true confounder if she scored eczema severity. However, the outcome (SCORAD) consists of maternal score (SYMPTOMS) and observer's score (SIGNS SCORE). Therefore the maternal eczema would not be independently related to disease severity in children. However, the child's eczema severity could be a consequence of the fact that the mother had eczema. The latter, therefore, is not a real confounding factor because it was not independently related to both the exposure (onset during the first year) and outcome (disease severity). Onset of eczema during the first year of life was a predictor of severe disease, which may imply that factors acting in utero or during the first year of life had affected disease severity. Longer follow-up studies are needed in order to measure the association over a longer period, for example the effect on adulthood eczema and to answer the question, does this association remain the same or does it change?

4.2.2.1.2 Ethnic group

4.2.2.1.2.1 Black skin

This study showed that black children who lived in London were at higher risk of severe atopic dermatitis than their white counterparts. It also showed that the significant difference in disease severity could be masked by reliance on erythema scores.

The proportion of white children in this sample was slightly lower than reported in the 1991 Census. For example, the percentage of white children in Lambeth, Southwark, and Lewisham was 69.7%, 75.6%, and 78% respectively (Balarajan and Raleigh., 1992) compared with 51% in the urban population recruited from the same areas. White children may be underrepresented in this population, but in the Lambeth area for example, AD is more common in black Caribbean children borne in the United Kingdom (16.3%) than their white (8.7%) counterparts (Williams, *et al.*, 1995a). Therefore, in a representative sample of children with atopic dermatitis one would expect a slightly higher proportion of black children than that reported in the 1991 Census. Thus the sample appears to be representative of the studied population and bias toward overrepresentation of black children was less likely to affect this finding.

One drawback of this study was observer bias. The investigator could have given children with black skin a high score, an outcome that was inevitable in such a study design. However, when parents' grading of disease severity on a 0 to 10 scale was used, black children remained at significant risk of having more severe disease than their white counterparts. This suggests that observer bias was less likely to have happened.

Parents' assessment of eczema severity may have eliminated observer bias but one should also think of a different source of bias in which parents of black children may have given higher scores to their children's eczema than white parents. Also, atopic dermatitis has some different clinical presentations in black children where extensor and papular lesions more common, but all the parents were aware that the study was looking at factors that might affect disease severity and there was no reason why parents of

black children would have been more likely to give high scores. Thus the chance of giving high scores among black and white would be the same. This can be supported by the observation that the risk remained highly significant even after controlling for potential confounders such as social class and area of residence. Another observation from this data supporting this interpretation was that parents' scores were significantly correlated with the observer's score at each visit (Table 18). This positive significant correlation means that parents and investigator agreed on disease assessment, which validated the parental score despite the difference in ethnic background. Measurement bias, therefore, was unlikely to have occurred and the finding was real and not biased, but it contradicts the finding of Williams *et al* (1995a). They reported no difference in the disease severity between black Caribbean and white children. Direct comparison cannot be made because the authors did not mention specific details about how the dermatologist assessed disease severity. Also the cross-sectional design of Williams' study cannot be compared with the longitudinal design implemented in this study.

Although it has been reported that the prevalence of flexural eczema or a history of this condition was lower in the Caribbean countries than in the UK (Pearson., 1973), data about disease severity were also lacking, therefore direct comparisons are not possible.

Factors associated with urbanisation may be important in AD prevalence and severity, but it cannot explain the difference in disease severity between black and white children who were born and lived in the same area. Genetic factors are more likely to play an important role in this disparity than environmental factors. It is probable that the latter acting together with genetic factors. This could mean for example, that black children are

genetically capable of making large amounts of IgE. This view could be supported by observations of an inverse relationship between helminth infestation and allergic diseases in the Gambia (Godfrey., 1975).

The literature provides little information about atopic dermatitis severity. However, the ethnic difference in disease severity has been documented in patients with asthma where blacks had much higher mortality rates than whites (Sly and O'Donnell., 1997). Although the exposure and outcome are different, Sly's finding is similar to this study. These authors found that uncontrolled and severe asthma had led to an increased mortality rate in blacks compared to whites.

Other social factors such as degree of exposure to pet allergens and differences in access to medical care may also explain this trend. In the current study, the fact that 50% of black children's parents were unemployed compared with 10% of parents in white children would rank most of the black children in a lower social class. Unemployment may have subjected children to inadequate medical care. In the United States, it has been reported that higher asthma morbidity and mortality were observed in the African American population. The higher risk was related to higher exposure and sensitisation to allergens from cockroaches, which are more prevalent in a lower social class environment (Togias, Horowitz, Joyner, *et al.*, 1997).

In the current study of AD though controlling for social class did not affect the outcome. Data on the potential difference in feeding habits, breast-feeding, type of heating, fitted carpets in the house and pets in the house could not explain the significant association between black skin and severe atopic dermatitis. The finding from this study adds strength to the need for further

genetic and epidemiological studies to confirm these results and thereafter a better understanding of atopic dermatitis.

The other aspect related to black skin was erythema scoring. The study has shown that reliance on erythema scores can mask severe atopic dermatitis in black children. Erythema is one of the components in almost all the scoring systems used to measure atopic dermatitis severity. Atopic dermatitis severity scores in clinical trials or observational studies, especially in areas inhabited with high percentages of ethnic minority groups, should be interpreted with caution because erythema scores can mask severe disease in black children. Thus GPs and dermatologists should note that the use of erythema in any severity system could be misleading in black children. Difficulties of assessment due to skin pigmentation might mean that severe cases are not being detected and appropriately treated.

Although it has been suggested that skin darkening should be used instead of erythema in pigmented skin (Kunz, *et al.*, 1997), the differences in healing time and pathophysiological process (erythema vs. hyperpigmentation) would make clinical comparison meaningless. Berth-Jones (1996a) suggested omitting erythema from the SASSAD in pigmented skin and reported that he was able to score erythema in Asian skin. The recent scoring system (NESS) from Nottingham (Emerson, *et al.*, 2000) has got around this problem in intensity assessment, but erythema scoring would meet the same problem when it comes to assessment of the extent of the examined eczema on the proposed 45 areas. Lichenification and papulation can be easily scored in pigmented as well as in white skin. Therefore these signs may be of help in clinical trials where the studied population contains a high proportion of those with pigmented skin. Further studies are needed to find an objective marker

for disease severity that does not depend on erythema scores and is valid in different ethnic groups.

4.2.2.1.2.2 Other Ethnic groups

There was small number of children from Asian and other ethnic groups. According to the 1991 Census, however, Asian and other ethnic groups represent a small percentage compared to blacks in the area studied (Balarajan and Raleigh., 1992). Therefore the sample is representative of the group living in the area studies and the small number of other ethnic groups was not due to selection bias and too small to allow any conclusion. However, in Leicester, it was reported that there was no significant difference in the prevalence of atopic dermatitis between Asian and white children (Neame, Berth-Jones, Kurinczuk, Graham-Brown., 1995). Areas with large Asian communities such as Brent, Tower Hamlets, Birmingham or Leicester (Balarajan and Raleigh., 1992) might be ideal places to study the difference in disease severity between white and Asian children. Studying different groups may help in exploring unidentifiable beneficial factors that may help in disease prevention. However, the lack of genetic markers for atopy, atopic dermatitis, and disease severity is an obstacle that needs to be overcome before more progress can be made in this field. Thereafter, comparing different ethnic groups can be a powerful indicator of the contribution of genetic versus environmental factors in AD aetiology.

4.2.2.1.3 Child's atopy

The study had shown that children with any atopic disease (asthma and/or hay fever) were at increased risk of having severe disease. But was there a chance that children with AD who had asthma and/or hay fever were more likely to participate in this study? This was unlikely to occur because the

frequency of atopic diseases (45% for hay fever, 43% for asthma, and 64% for any atopy) in this study was similar to the frequency of atopic diseases in atopic eczema documented in other studies. It has been shown that around 50% of patients with AD have other atopic diseases (Rystedt., 1985; Rajka., 1989a; Aberg and Engstrom., 1990; Williams, et al. 1996). A recent study from Sweden where children with AD were followed up, it has been reported that 43% developed asthma and 45% allergic rhinitis (Gustafsson, *et al.*, 2000). Therefore information bias was unlikely to have occurred. Nevertheless, in an individual patient the course of atopic cutaneous or respiratory manifestation may be alternating, simultaneous, or independent (Rajka., 1989a).

Therefore this finding confirms that any atopic disease (asthma and/or hay fever) in a child was significantly associated with more severe AD, with hay fever as the dominant significant effect. However, the risk of severe disease in children with asthma became marginally statistically insignificant ($p = 0.07$) after adjusting for hay fever, compared with those without asthma. So is hay fever a true confounder or not? It is part of exposure (atopy; eczema, hay fever and asthma) and may be associated with the outcome (AD severity). Hay fever does not appear to be a true confounder because it forms part of the exposure and is not independently associated with the exposure. Therefore the adjustment for hay fever cannot be justified, and asthma had a real association with disease severity. The findings are in accordance with those of Musgrove and Morgan (1976) from a historical cohort study, in which they showed that the persistence of eczema was greater in those who had asthma and/or hay fever. Rystedt (1985) has found that associated allergic rhinitis, and/or bronchial asthma were unfavourable prognostic factors for

healing of AD. The finding that hay fever had an independent effect on disease severity is in agreement with Rystedt's findings that allergic rhinitis had the dominant effect of these two factors (Rystedt., 1985). However, she used the number of sites as a measure of dermatitis severity. Vickers (1980) has shown that the prognosis appeared to be slightly worse when the patient had classical bronchial asthma but hay fever and urticaria, when present, did not influence the prognosis at 10 years. Most of these studies looked at the prognosis of AD using a completely different design and were mainly based in a hospital setting. Although, these findings are in agreement with that of the current study, direct comparison would not be sensible because of the differences in inclusion criteria and assessment of outcome.

This is an important clinical finding for clinicians and researchers. First, clinicians should be aware that children with hay fever and/or asthma tend to have severe atopic dermatitis. This may help them in managing such cases and may explain why the usual remedies may not work. Second, in clinical trials these subjects should be analysed separately. The observation that hay fever and/or asthma were predictors of severe disease necessitate controlling for them and carrying out a sub-analysis of the data before concluding whether a particular drug was effective or not.

4.2.2.1.4 Sex

Sex and disease severity were not associated and this relationship remained insignificant after adjusting for potential confounders. Queille-Roussel *et al* (1985) also reported no difference in disease severity between males and females. On the other hand, Rystedt (1985) reported an increased risk of severe disease among female patients. Disease severity assessment in her study was based on an arbitrary scoring system that has never been validated, and which is less standardised than the system used in this study. The age difference and hospital origin in her study may explain the incongruity between this study and Rystedt's (1985) study.

It is also possible that there was an observer bias. This highlights the need for objective markers of disease severity and further studies where the observer shouldn't be aware of the outcome of interest. In conclusion sex seems to have no significant association with disease severity.

4.2.2.1.5 Birth Weight and Gestational age

Birth weight has no significant predictive value for AD severity. Although the birth weight was not matched for gestational age, the latter was treated as a potential confounder and controlled for by regression analysis. Gestational age also seems to have no significant association with disease severity. One drawback is that information about gestational age and birth weight were obtained retrospectively from the parents with a minimum 5 years recall time, perhaps more, and not from the maternity records. This may have affected the accuracy of the information in which parents could not remember the exact gestational age or the birth weight. Such bias is possible, but for example the reported gestational age was 37 weeks or more in 90% of children, which was comparable with a study from Manchester where 97% of

children were born in the same gestational age group (David and Ewing., 1988). This suggests that information bias was unlikely to have occurred.

This study finding interestingly contradicts with Davis and Ewing's study (1988), in which they reported that the possible chances of the subsequent development of severe disease was reduced by preterm birth. Although the former study has a similar percentage of exposure, the outcome assessment "severe atopic eczema" was not reported at all. They did not give any information about how they assessed disease severity nor how it was assessed. The study design was another drawback of David and Ewing's finding (1988) because it was not clear whether a retrospective or prospective design had been implemented, though it is likely to have been retrospective. In the current study the exposure and the outcome were both reported in detail and therefore neither birth weight nor gestational age had any significant predictive value for severe disease. Given the possible risk of information bias and the statistically insignificant associations, these factors will not be discussed any further.

4.2.2.1.6 Child's age

An increase in the child's age has a non-significant association with disease severity and remained the same after adjusting for potential confounders. However, the short follow-up time of this specific age group, within the studied sample, necessitate interpreting this finding with some caution. Thus it does not necessarily mean that AD severity does not change with age. This speculation is supported by the highly significant improvement in disease severity ($p < 0.001$) when the parents assessed atopic dermatitis in the children. This suggests that eczema does improve with age. Although the

parents' assessment was more subjective and retrospective with different recall times, it indicated real and significant improvement in disease severity. However, when the sample was divided into two groups, the study showed evidence of lower risk of disease severity in the older children but this was not statistically significant. Furthermore, this insignificant result does not mean that there is no real association of age with disease severity but only that the data are compatible with there being no association.

Therefore, a longer follow-up time is needed before reaching a firm conclusion regarding the relationship between age and atopic dermatitis severity. Re-examining the same population after 10 years might give a better answer as to the association of age with disease severity.

4.2.2.1.7 Family Size

An increase in the number of children in the family was also not significantly associated with disease severity. Data on the age of siblings were not available and therefore it was not possible to investigate if older children in the house had different effects. The exposure status was not biased because the mean and median of the number of children were similar to the national average of 2.4 children per family. However, this finding cannot be directly compared with the inverse association between prevalence of reported AD and family size that was documented from the National Child Development Study (Strachan., 1989) because the former study looked at disease prevalence and disease severity was the outcome of interest in the present study.

Therefore family size and disease severity were not significantly associated and in the absence of any study looking at the same outcome it will not be discussed further.

4.2.2.1.8 Parental atopy (eczema, asthma, or hay fever)

The study showed no significant predictive value of parents' atopy for disease severity. This might be due to information bias because there were more data missing about paternal than maternal atopy, which can be explained by the fact that more mothers had completed the questionnaires. In general the mother may have been unlikely to know whether her husband or partner had had atopic disease as a child.

Recall bias also cannot totally be excluded. It has been documented lately that recall bias should be considered for any association between parental and child's atopy. In simple terms parents would be more likely to report atopy when their children develop an atopic disease (Kulig, *et al.*, 2000). Information bias cannot be ruled out from the data available. The discussion of parent's atopy therefore will be brief.

4.2.2.1.8.1 Parents' Eczema

The study showed that children whose mother had eczema were at a non-significant lower risk of severe disease than those whose mothers never had eczema. However, information bias might have influenced this association and the data available cannot confirm whether the association is real or not. If information bias had no influence then the effect of the mothers' eczema on lowering disease severity was real. One potential explanation could be that the mother who had eczema has more experience of taking care of AD, in terms of avoiding irritants, applying moisturiser and early recognition of disease and the appropriate application of steroid creams. The mother may have modified the environment because of her awareness of her own eczema, and this ultimately would lead to the child living in a predetermined environment. Change in environment may explain the positive association

with disease severity, but it would have no effect on genetic predisposition. Another potential explanation that mothers may have intentionally or unintentionally blamed fathers for passing the disease to their children and, therefore, may have overestimated eczema in fathers. Further studies are needed to examine the association of maternal of eczema with disease severity. A valid definition such the UK diagnostic criteria could be used to identify eczema in potential mothers and then these could be followed-up prospectively to assess the association with their children's AD severity, if they developed AD. Such information is needed for a better understanding of AD and may help in treatment and prevention. It could mean that educating the mother might help in lowering disease severity. However, such a study would take many years to complete.

4.2.2.1.8.2 Parents' asthma and/or hay fever

There was no evidence from this data to support any association of parental asthma and/or hay fever with AD severity in their children. The high risk of information bias regarding these factors made further interpretation unhelpful.

4.2.2.1.8.3 Paternal and maternal atopy

The study showed a non-significant increase in the risk of severe AD in children when the mother or the father had any atopic disease. The high potential for information bias has limited any further conclusion, even though, in a study looking at disease expression, it was shown that maternal atopy resulted in a higher risk of infantile atopic dermatitis than paternal atopy. This group investigated disease prevalence during the first year of life and identified atopy in parents by skin test to common inhalant allergens (Ruiz, Kemeny, Price., 1992). The small amount of each exposure, in this study, did

not allow the investigator to determine whether maternal atopy had the same association with disease severity or not.

With limitation in the knowledge about disease severity this finding should be taken with the above-mentioned restriction and attention should be directed to eliminating any information bias in future studies.

4.2.2.2 Extrinsic factors

4.2.2.2.1 Area of residence

The study has shown that the risk of severe disease was about two times higher in children with atopic dermatitis who live in an urban area, than those who live in a rural environment. A recognised difficulty in such studies was to make the observer blind to the exposure, which was totally impossible in this study design. This did not affect the outcome because the risk remained significant even when three different ways of severity assessment were used. Observer bias therefore was less likely to have happened, even though it cannot totally be excluded.

A potential reason for this difference in disease severity might be the differences in air quality or exposure to allergens or infection in the rural environment. Another factor could be the differences in water supply between the two areas (McNally, Williams, Smallman-Raynor, *et al.*, 1998). Certainly life styles in the cities have changed dramatically in the last 50 years. Double glazing, fitted carpets, heating and car pollution have changed and all are associated with urbanisation. This change in the cities may explain the increased prevalence in AD, but further studies are needed to quantify any difference in potential risk factors such as car emissions and water constituents.

The difference in ethnic background cannot explain this disparity because in the current study when all children from the rural area were excluded, black children with atopic dermatitis remained at higher risk of severe disease than their white counterparts live in the same (urban) area. On the other hand, when blacks were not included in the comparison between urban and rural areas, children living in the urban still have higher risk of severe disease than their white counterparts.

Although Poysa *et al* (1991) reported an increased prevalence in the urban area, to the investigator's knowledge no one has reported an association of an urban area with atopic dermatitis severity. However, further studies that include information about water supply and air pollution might be needed before a valid explanation for this disparity can be achieved. Such a study should also be able to identify the differences in allergens such as house dust mite and pollens and therefore might have an important implication for a better understanding of this disease.

4.2.2.2.2 Food

Children were more likely to have severe disease when their parents were aware of a food source that made the children's eczema worse than those whose parents were unaware of any kind food effect, which became statistically insignificant after adjustment. This could represent a real effect of food in enhancing flare-up of the disease or just that parents of children with severe disease were more likely to provide a reason for eczema worsening. Information about the exposure was collected retrospectively. It was very probable that the parents of children with severe disease are more likely to be concerned with the cause of the disease, and therefore more likely provide a reason for the exposure to potential risk factors. It is difficult to

refute the possibility that the higher risk of severe disease after exposure to certain type of food is a result of recall bias. Although this finding is somehow similar to Guillet and Guillet's study (1992), the assessment of exposure in the former study was completely different. The current study used questionnaires while the other used skin test with fresh food allergens and standard extracts. Therefore these two studies cannot be compared but Guillet and Guillet's study (1992) seems to provide evidence for a role of food in atopic dermatitis especially the severe form where all the children were 100% positive to food tests.

The current study finding is based on an observational design, but blind systematic evaluation based on food challenge could confirm the relationship between food and eczema severity, and therefore a double-blind placebo-controlled oral food challenges (DBPCFC) might be an ideal way of looking at any food association with disease severity. Thereafter would be possible to identify those subjects who could benefit from diet restriction. Nevertheless, Atherton et al (1978) suggested, from a double-blind controlled crossover trial, that diet might have an effect in controlling atopic dermatitis (Atherton, et al., 1978), but a recent review on the role of diet in atopic dermatitis concluded that there is no evidence for the role of dietary elimination in the management of AD (David, et al., 2000).

Therefore the effect of food on AD remains controversial and the current study approach seems to be practical and useful in exploring the relationships between food and eczema severity, and further studies such as (DBPCFC) are needed to confirm or refute this finding.

4.2.2.2.3 Wool

It was shown that children who had reacted to wool were about two times more likely to have severe atopic dermatitis than those who had not reacted. The association became statistically insignificant after adjustment for area of residence. It seems that the urban area still hold the statistically significant higher risk of severe disease. However, the information about reaction to wool was collected retrospectively, and a greater reporting of sensitivity to wool by parents of children with severe disease, compared with those with less severe disease as with diet, cannot be dismissed as a possible source of bias. It could be a real effect of wool in enhancing flare-up of the disease or just that parents of children with severe disease were more likely to answer yes. Collecting data about wool is subject to the same limitation as collecting data about food. Both factors have the same tendency to information bias.

The potential information bias and the statistically insignificant higher risk after adjusting for area of residence would suggest that wool does not have real effect on disease severity and therefore its effect might be considered as happening by chance. Nevertheless, this finding could imply that wool contains antigenic material such as lanoline that triggers and exacerbates the disease. Prick and patch testing, in double-blind controlled study design, should be done to confirm this hypothesis. It would be interesting for instance to prick and patch test this population plus a control group with wool allergens and see if they have the same trend.

4.2.2.2.4 Breast feeding

Breast-feeding had no significant association with disease severity. The long recall may have affected the accuracy of the exposure. In this study about 70% of children were breast-fed, similar to another study looking at predictors

of AD prevalence where 66% of children were breast-fed (Berth-Jones, George, Graham-Brown., 1997). Thus information bias was unlikely to have affected the outcome and therefore it is safe to conclude that breast-feeding had no significant effect on disease severity.

4.2.2.2.5 Social class

Social class seems to have had no significant association with disease severity, but was the exposure biased? Although direct comparisons cannot be made, the social class distribution in this population was similar to that reported in the 1971 census in which the majority were in social classes III and IV (Leete and Fox., 1977). However, the overrepresentation of, social classes I and II in this population could be explained by the increased prevalence of AD among these classes (Williams, *et al.*, 1994d). This suggests that the social classes in this population were representative and that exposure bias was less likely to affect the results. The finding that there no association between social class and disease severity should stand.

Although data on AD severity is scarce, a recent study investigated the effect of social class on the severity of respiratory symptoms in asthmatics in a cross sectional survey of two general practices in Staffordshire (one urban and one rural). They showed that responders from social class V were more likely to report severe respiratory symptoms than those from social class I, and that these were independently related. The location of the general practice was not independently associated with the severity of respiratory symptoms (Trinder, Croft, Lewis., 2000).

Further research is needed to rule out an absence of effect or to exclude any clinically important difference in atopic dermatitis severity between higher and lower social classes.

4.3 Section 4: Quality of life

At the time of writing, and to the best of the my knowledge, there are no other published clinical-epidemiological studies, which have related children and family's quality of life to atopic dermatitis severity in children in a systematic way, as a cross-section and over a time period, from a community-based study.

4.3.1 Family' Quality of life

4.3.1.1 The total DFI on visits one and two

The study examines families' quality of life scores for children with atopic dermatitis in a community-based study at baseline (visit 1) and at 6 months (visit 2). Family's QOL was affected in the households of 45% and 33% of children during the first and second visits respectively. This confirms the impact of mainly mild childhood atopic dermatitis on the family on each occasion. It was also shown that the family's quality of life was significantly correlated with atopic dermatitis severity in the children at a point in time and after 6 months.

The DFI is an instrument constructed to evaluate the impact of AD on the family by the parents (Lawson, *et al.*, 1998) and the SCORAD was developed to assess AD severity by objective means (European Task Force on Atopic Dermatitis., 1993). It is interesting though to see that in this study the two different systems scored by different observers produced parallel results. One negative point, relevant to this and other studies in atopic dermatitis, is that there is no other standard objective marker for disease severity, such as a serological response, which could be compared with the SCORAD-D. However, in the absence of such a marker, using a measure such as the

SCORAD, which has proven usage in the assessment of atopic dermatitis severity in a population-based study, seems to be a reasonable approach. This finding confirms the suggestion that stress and family environment are related to symptom severity in children with severe atopic dermatitis from a hospital-based study (Gil, Keefe, Sampson, *et al.*, 1987).

The current study's finding that the DFI is related to severity of the child's AD supports the construct validity of the DFI. It is also in agreement with Lawson's finding (1998) when the DFI was developed. They showed that the severity of the child's AD and the severity of disturbance in the family were related ($r=0.55$, $P=0.002$) (Lawson, *et al.*, 1998). When the DFI was first tested, the mean DFI score was 9.6 (SD = 7.0, median = 9.5), and in our study the mean was 2 (SD = 4, median 0.5). This difference can be explained by selection of patients (hospital versus primary care). Also, Harper *et al.* (2000) reported, using a different study design (a prospective, randomised, open, parallel group, multicentre oral cyclosporin study), significant improvement in family quality of life and disease severity after treating severe childhood atopic dermatitis with oral cyclosporin (Harper, *et al.*, 2000). They did not report however whether these significant improvements are related or not.

Although the proportion of disease impact differs between children and parents, there was significant correlation between children and family's quality of life scores. This may imply that they were assessing the same problem but had perceived it with varying intensity, a reasonable supposition. Another finding from this study, which supports the internal consistency of parents' assessment of quality of life, was the significant correlation between the DFI and parental assessment of disease severity. It shows that parents

were consistently able to evaluate disease status. despite the fact that they used two different approaches. This finding was also reported from a recent study to develop a new questionnaire to measure the impact of infantile eczema on the family (Lewis-Jones, Finlay, Dykes., 2001). The correlation coefficient was 0.50 and 95%CI 0.32 to 0.64, which is obviously statistically significant and similar to the current study correlation coefficient.

Finally, one important point that should be remembered is that the SCORAD-D represents disease severity at a certain point of time in that particular day and the DFI was designed to measure the impact of childhood eczema in the last week, but any effect before this week cannot totally be excluded. Therefore this may explain the weaker association. Theoretically the association could become stronger if the family's QOL could be measured at the same time as disease severity, a view supported by the slightly stronger and highly significant relation between the CDLQI and DFI, in which both instruments have the same recall time.

4.3.1.2 The DFI at visits one and two by site

The DFI scores were, whether mean or median was used, higher when there was visible eczema on both visits. Although visible eczema was associated with non-significant higher scores on the DFI, the results were not shown because it was thought that eczema at any site could confound this finding and it was not possible to provide a meaningful control. However, this is the first time, in childhood atopic dermatitis. that the impact of visible eczema on the family's quality of life has been demonstrated. The usefulness of the DFI was shown by its' ability to give higher scores to children with visible eczema than those without visible eczema at a particular site. The finding has

demonstrated the construct validity of the DFI and this may contribute to the estimation of power and calculation of sample size for clinical trials.

4.3.1.3 Each aspect of the DFI on visit one and two

Childhood eczema had affected different aspects of the family's life. It was very difficult to make any direct comparison between other instruments and the DFI because the latter is a disease specific measure. However some problems documented here have been reported by other studies, for example, sleep disturbance was reported by 86% of the parents with an average of parental sleep loss of 2.6 hours per night (Reid and Lewis-Jones., 1995). The high percentage of parental sleep loss was perhaps due to inclusion of severe AD from the out-patient clinic. The lower percentage in this study (22% and 16% at visits, one and two respectively) could be explained by the inclusion of mild cases from a community setting. This was supported by data from this study, in which disease severity had a significant association with the score on the effect of eczema on the sleep of other members of the family at both visits. Differences in the specific outcome between this study and Reid's study (1995) could be the reason for the disparity. In Reid's study, the impact of eczema on parents' sleep only was measured, while in this study the question included the effect on the other members of the family.

However, whether the study is based in hospital or the community, there is a clear impact of eczema on the families' sleep. It is necessary to document this impact and therefore to have a treatment strategy that takes into consideration improvement of the families' sleep patterns. It also may help in influence involvement of a psychiatrist and psychologist in the management of some cases of AD, mainly aiming at relieving the stress that originates

from sleep loss. Clinical trials should include assessment of family sleep loss in outcome measures because this will show disease improvement from a different point of view.

In 20% and 17% of children with AD, the cost related to treatment and/or clothes had also been affected. This shows that even mild eczema can affect the expenditure of the family and cause an extra burden on household expenses.

4.3.1.4 Changes in DFI and SCORAD-D scores over 6 months

This is the first time in the study of childhood atopic dermatitis that changes in family quality of life can be related to changes in disease severity in a community-based epidemiological study. There was no significant difference in family's quality of life nor in disease severity between the two visits. It is to be expected that there would be no significant change in the average level of disease severity or impact on family quality of life, as this is a non-progressive disease with recurrent flare-ups.

The interpretation of the regression coefficient should be explained here: The initial means of the DFI and SCORAD-D were 2.4 and 8.2 respectively and six months later the mean final DFI and SCORAD-D were 1.9 and 7.7 respectively. The ratios of the mean DFI to the mean SCORAD-D are 3.4 and 4 on the first and second visit respectively. The maximums are 30 for the DFI and 72.5 for the SCORAD-D, ratio 2.4. This means that 1 unit of DFI was related to more than one unit of SCORAD-D and the effect of SCORAD-D is therefore rather stronger than the regression coefficients imply. This serves to emphasise that these are substantial effects on the family's quality of life.

However, individual patients experience flare-ups that come and go between the repeat assessments. It is the impact of these flare-ups on the life of the

families that is measured by the association between changes in SCORAD-D and DFI. Changes are harder to measure accurately than individual scores. The association between SCORAD-D and DFI is of a similar magnitude (0.21 rising to 0.37 DFI points for each additional SCORAD-D point for each unit) as that between the changes (0.17 DFI per SCORAD-D unit), with broad and overlapping confidence intervals. The data therefore do not allow us to conclude that the association is weaker for changes over time than for single scores. The fact that the changes between the visits were not significant strengthens the finding rather than undermine it.

Thus the study showed a non-significant improvement in disease severity and family's quality of life. There were mild changes toward improvement and these changes were significantly associated. In other word, it means that the two parameters changed in the same direction (getting better). This suggests that the DFI had the ability to detect minimal changes in disease severity. This approach could be used in clinical trails where the disease severity expected to drop sharply.

Although this is the first community-based study on atopic dermatitis in children to relate changes in family quality of life to changes in disease severity, the study findings are consistent with another study in asthma that has shown that changes in Asthma Quality of Life (AQOL) correlated with changes in symptom score and bronchial hyperreactivity (Marks, Dunn, Woolcock., 1993).

Nonetheless, it cannot be assumed that the ability of the DFI to detect decreasing scores (getting better) necessarily means a similar ability to detect increased scores (getting worst), although there is no real reason why the DFI should detect changes in one direction and not the other. Since it is

an observational study and only a small number had deteriorated, it was not possible to investigate the responsiveness of the DFI in the other direction. Nevertheless, this may not have fundamental implications against using the DFI because the DFI would be used in clinical trials where the aim would be to detect decreases in the score rather than an increase.

4.3.1.5 Changes in the DFI Components and SCORAD-D over 6 months

There was evidence to suggest a significant relation between changes in disease severity and changes in the impact of eczema on family leisure activities. This implies that the effect on duration of leisure activities will vary with the changes in disease severity. But this finding may not be important clinically as it may represent seasonal variation because the final visit was preceded by the summer holiday.

The weak strength for the association could be explained by the difference between the high scores for the SCORAD-D (72.5) and the DFI component (3). The maximum score of the SCORAD-D is about 2.5 times higher than the total DFI and about 24 times more than each score of the DFI component.

Changes in expenditure score were not significantly related to changes in disease severity. This might be explained by the observation that the expenses are still the same, or that parents are spending the same amount of money to keep eczema under control, even if the severity had improved slightly. Another explanation might be the high proportion of mild cases in this population.

In general changes in the other DFI components were not significantly related to changes in SCORAD-D. The observational design of this study and short follow-up time (6months) could explain the non-significant association.

The former perhaps did not allow a real relation to be shown to be significant. Therefore investigating the relationship between these variables such as cost and impact on carer's lives may need a longer time before a firm conclusion can be reached.

4.3.2 Children's Quality of life

The study has shown that children's QOL was affected in the majority of children. There are important reasons for asking the children about their health status and QOL, in order to provide information that is not generally available from a physician's assessment or by asking the parents. Such information is important in portraying the morbidity caused by atopic dermatitis and to evaluate the effectiveness of health and health-care interventions. It is therefore valuable to collect information, when possible, directly and independently from the children themselves.

4.3.2.1 Completing the CDLQI

Thirty-three per cent and 25% of children were unable to complete the CDLQI at visit one and two respectively. The mean age of those unable to complete the CDLQI was lower than those who completed the questionnaire. Potential reason for not completing the CDLQI might be due to the restriction that was applied in the study design. When the questionnaire was first designed, an adult, preferably the child's parent was allowed to help the child in completion of the questionnaire (Lewis-Jones and Finlay 1995). In this study parents were not allowed to help their children in completing the CDLQI because the effect on children themselves ought to be quantified without any influence. Parents also had completed the DFI to document the impact on the family, which could affect their way in which they answered questions

regarding their children. The children who participated in this study aged 5 to 12 years may also have had a different perception of life from their parents. This was supported by the different impact on the quality of life: on the first visit for instance 45% of children's families were affected when assessed by the parents, while 92% of children were affected when assessed by the children themselves. The impact on quality of life was two times higher when children assessed quality of life than parents' assessment. Therefore children were able to recognise features that were seen by the parents as unimportant.

It is quite clear that the restriction implemented in this study had affected the ability of the young children in completing the CDLQI than older children, which could have been improved by reading the questionnaire to young age group or allowing the parents to help in completion. This would have improved the number but would have introduced a different observer and ultimately could have introduced information bias. Therefore the data obtained by applying this restriction is of the same quality and justify the restriction.

Nevertheless, one might speculate that this could have biased the results. The speculation would be that intelligent young children who completed the CDLQI had more severe disease than those who could not complete the CDLQI and therefore were more likely to complete the CDLQI. For instance, in this study, the youngest age group was 6 years old and there were 28 children in this category, of these a high percentage (82%) was unable to complete the CDLQI. To evaluate if there was substantial difference in disease severity between these two groups, the objective severity scores for these children were compared. The mean SCORAD-D was 8.0 for the 5

children who completed the CDLQI and was similar to the mean SCORAD-D (8.4) for the 23 children who were unable to complete the CDLQI. This suggests that the speculation that children with more severe disease were more likely to complete the CDLQI is not true. The percentages of children who completed the CDLQI in the 7 and 8 years categories were higher and bias due to those subjects being able to complete the CDLQI was less likely to influence the conclusion.

It is also important to mention that the restriction was implemented before carrying out the analysis. This in itself would exclude any potential bias as any child in that particular age group stand a same chance of completing the CDLQI. It can be concluded that the restriction implemented in this study did not have any substantial effect on the conclusion.

The differing reading ability between children in different social classes, ethnic background or area of residence might be another potential reason for the children not completing the CDLQI. However, data from this study did not show any significant difference in these factors between those who did and did not complete the CDLQI.

4.3.2.2 The total CDLQI on visits one and two

In this study 78 and 90 children from a primary care setting were included on the first and second visits respectively. This is nearly double the number of children with eczema (47) used in the preliminary validation of the CDLQI from a hospital based-setting (Lewis-Jones and Finlay 1995). In general, atopic dermatitis had affected the QOL and was scored at more than zero in 92% and 79% of children during the first and second visits respectively, despite the fact that 44% and 48% of children were free of eczema during the same time. It can be concluded from this finding that children's quality of life

was affected even when there was no visible eczema, which is to be expected in a chronic relapsing disease such as atopic dermatitis. Another inference that can be drawn from the former finding was the difference in evaluating the significance of the problem by observer and children. Physicians should be aware that their assessment of signs does not necessarily reflect a comprehensive evaluation of patients' quality of life. Therefore, doctors should always assess, value and consider the patients' assessment during their consultation.

The mean scores of the CDLQI in this study were lower than the mean scores in the initial validation of the CDLQI (Lewis-Jones and Finlay 1995). The latter findings were based on many different skin diseases from an outpatient department. The mean score was 7.7 (SD = 5.6) for children with eczema (Lewis-Jones and Finlay 1995). The source of cases, hospital versus community, may explain the disparity in the mean score. It has been reported that AD severity was associated with an increased referral rate to the hospital from primary care and therefore more severe cases were expected to be seen in the hospital (Emerson, *et al.*, 1998).

Theoretically patients with severe disease would be expected to have a higher impact on their QOL. This was shown by the highly significant and positive association between children's QOL scores and severity scores, which remained the same after controlling for potential confounders. This suggests a consistent association between the two instruments, one disease-specific (the SCORAD) measuring signs and another speciality-specific (the CDLQI) measuring the impact on QOL. Although there was a highly statistically significant correlation between the scores of disease severity and those of children's quality of life, the severity scores account for only 21%

and 28% in the variation of the children's quality of life score at the first and second visits respectively. Quality of life is a concept that includes in its assessment many subjective elements. It is, therefore, perhaps not surprising that the observer's assessment of disease severity could explain about one quarter of the variability in quality of life measures. This may be due to the difference in the duration of assessment, in which severity assessment reflects disease status at a certain point of time while the CDLQI measures the effect in the last 7 days. But, the more likely explanation is that an assessment of signs does not necessarily explore the impact of the disease on quality of life. It is, therefore, necessary to include a quality of life measure plus an (severity) assessment of signs in clinical trials because doctors may not have the required knowledge of the children's feelings to evaluate their quality of life accurately.

Some degree of caution should be exercised when interpreting the results of a study such as this. The population under investigation included those with wide range of eczema severities with a majority of mild cases. It is unlikely that the relationship between the CDLQI and disease severity will predictably remain the same in different disease severities. It may be strengthened or become weaker according to disease stage. However, part of the reason for such a study is to investigate if the quality of life instrument can add some information, which is useful, about the disease status that cannot be determined directly by the doctor. The CDLQI, therefore, proved to be useful in providing extra information about disease status as seen by the children themselves. Therefore quality of life instruments should be used as extra measures of assessing outcome in clinical practice, research and clinical trials.

Although the impact scored by the children was higher than by parents, the total CDLQI was significantly correlated with the DFI. This highlights the agreement on reporting the stress caused by this stressful disease, despite the differences in the strength of disease perception.

The study has shown that changes in children's quality of life can be predicted by changes in disease severity despite the difference in these two scores and despite the difference in these changes. The former finding highlights the importance of including quality of life assessment as an extra measure of disease assessment in clinical trials. However, one should bear in mind the following question:

Why was there a true significant improvement?

The significant improvement in the CDLQI could be biased by the second visit being preceded by long summer holiday or seasonal fluctuation of AD. The observational design and length of time between the two visits (6 months) may make any factor that had a statistically significant effect on a sense of well-being irrelevant clinically. The CDLQI reflects the child's own assessment of the disease whereas the SCORAD represents the observer's assessment of disease severity. This finding shows a significant improvement in quality of life and a non-significant one in disease severity. However, the 1.5 units decrease in the CDLQI that was statistically significant is not clinically important because by analogy this is similar to a statistically significant 5 millimetres mercury difference in blood pressure between right and left arm. These latter figures show a statistically significant difference but have no significant clinical implication.

Another explanation that these discrepancies may be due to the summer holiday i.e. reduced stress, different attitude that preceded the second visit,

or that the investigator, using the SCORAD, was unable to detect a subtle improvement in disease severity that seemed to be significant for the children. Seasonal variation in the disease cannot be ruled out.

4.3.2.3 The total CDLQI on visits one and two by gender

This study has shown no significant difference in the CDLQI scores between males and females in childhood atopic dermatitis. This finding could perhaps be explained by the similarity in life perception in the age group (5-12 years) studied. Studying a different age group for example 12 to 16 years or adults may show significant differences in quality of life between females and males, a finding that has been shown when the Danish version of DLQI was used to assess the impact of any skin disease on quality of life (Zachariae, Zachariae C, Ibsen, *et al.*, 2000). However, in studying adult populations with dermatological disorders recruited from a hospital outpatients department Finlay and Khan (1994) were unable to find any difference (Finlay and Khan., 1994). It should be emphasised that the two studies previously-mentioned used a different quality of life measure (DLQI) and the patients included were adults with different dermatological conditions. Therefore direct comparison could not be made because this study included children with one skin disease (atopic dermatitis) only. Investigating the effect of atopic dermatitis on quality of life during the teenage period may show a different result.

Male scores on the CDLQI had a stronger association with disease severity than female scores and severity scores could explain about 44% of the variation in male's quality of life score while disease severity could explain only 20% of variation in female scores. This may suggest that factors, such as impact on individual and body image, other than eczema severity may be important for females but not affect males.

There were no differences in the mean CDLQI scores between males and females except for teasing where it was significant during the second visit and not during the first. This inconsistent difference could not be explained by visible eczema. In theory, visible signs would be the main cause of the child being teased, called names, or bullied. Other factors such as a summer holiday and wearing different clothes and doing different activities between males and females may explain the inconsistent results.

4.3.2.4 Individual aspect of the CDLQI on Visits One and Two

Itching scores represented the highest proportion of the total CDLQI at each visit. About three quarters of children had an itchy “scratchy” or painful skin and this produced the highest overall mean score. This highlights how itchy AD is and the discomfort to the child from having this disease. Although direct comparison cannot be made between this finding and the original validation study, the trend was in accordance with the initial validation of the CDLQI. The highest mean score was for questions relating to symptoms (such as itching) and feeling, and the lowest for questions relating to friendships (Lewis-Jones and Finlay 1995).

There was a significant correlation between itching scores and observer’s scores of excoriation and lichenification. Although this association was statistically significant, the variation in observer’s scores could not explain more than 15% of the variation in the itching scores. Excoriation and lichenification are physical signs that appears as consequences of scratching and rubbing respectively. The positive but weak correlation between scratching scores and the observer’s assessment of excoriation and lichenification on each visit documented in this study is important. It means

that the observer was able to assess objectively a physical sign that has some effect on the child's life.

About one third of children were embarrassed by their eczema. Scores on the question related to being embarrassed or self-conscious, upset or sad because of AD, were significantly correlated to severity scores on each visit. The positive and highly significant correlation suggests that an increase in disease severity could lead to the child being more embarrassed, upset or sad. However, one should bear in mind other factors such body image, customs and personality that may affect variation in embarrassment scores because variation in severity scores could account for 12% only.

Finally, going out, playing or doing hobbies, buying special clothes/shoes, swimming or other sports, teasing, bullying, asking questions or avoidance by other people due to eczema, and an impact on friendships were not significantly associated with disease severity and will not be discussed further.

4.3.2.5 Collated scores of groupings of the questions at each visit

It was shown that the major impact of atopic dermatitis was on symptoms and on feelings, a finding in agreement with the original validation of the questionnaire (Lewis-Jones and Finlay., 1995). The CDLQI shows the same outcome in two different study setting (community versus hospital). This therefore provides evidence for the applicability and validity of using the CDLQI to assess quality of life to produce the systematic assessment of the effect of such a stressful disease on children' life and development.

4.3.2.6 Generalisation and extrapolation

Quality of life measurements are needed for assessment of new therapies. for audit purposes, and for medical plans to highlight the handicap caused by

skin disease when resources are being distributed. Quality of life measurement provides an understanding of the disease as seen by the patients, which may support the need for further research in atopic dermatitis, specifically, and dermatology generally. A valid and reliable measurement of quality of life may help in providing the justification needed for further research. It is clear from this finding that AD had affected the life of 92% of children in this study. Atopic dermatitis is a very common disease affecting not less than 10% of the UK population; therefore about 6 million sufferers with AD in the UK, and possibly more. In fact, 70% of AD cases are seen before the age of two. Given the previous two statements, 4,200,000 subjects would have had eczema during their childhood. Of these 4,200,000 cases, 92% had an impaired quality of life and possibly abnormal behavioural development. Hence about 3,750,000 (6.25%) of the UK population have an impaired quality of life due to eczema alone.

This may justify our claims as dermatologists for further research and redistribution of resources and may help in flagging the burden caused by the disease that not has a priority by the fund holders.

4.4 Section 4: Conclusion

4.4.1 Course of AD

Parents' assessment of AD severity has shown that there was a highly significant improvement of disease severity by age. Summer was the best season for children's eczema in 38% of children and most (90%) had applied topical steroids before joining the study. Increased frequency of topical steroids occurred with increased disease severity. The observer assessment of disease severity was higher in those receiving systemic antibiotics and oral prednisolone, while the scores were nearly the same in those using oral antihistamines. However, parents score of subjective symptom was higher in those taking oral antihistamines than those who did not take them.

4.4.2 Disease severity

This longitudinal study of children with atopic dermatitis showed that onset of eczema during the first year of life, asthma and/or hay fever (atopy) in the child and living in an urban area was associated with more severe disease. Black children also were at higher risk of severe disease than their white counterparts and reliance on erythema scores can mask this higher risk of severe disease.

Certain types of food and reaction to wool were significantly associated with severe disease. However, the risk became insignificant after adjusting for potential confounders. Information bias also cannot totally be excluded. Therefore the association between these two factors and disease severity remains to be confirmed.

Family size, sex, birth weight, gestational age, child's age, any atopy (hay fever, asthma, or eczema) in the parents, social class, breastfeeding and any atopy in siblings were not significantly associated with disease severity.

4.4.3 Quality of life

The impact of atopic dermatitis on quality of life was documented by using the DFI and CDLQI. The study has showed that childhood atopic dermatitis had a remarkable effect on both families and children's and quality of life. Family's quality of life was affected in the household in 45% and 33% of children during the first and second visits respectively according to parents' assessments. Quality of life in 92% and 79% of children was affected during the first and second visits respectively when the children had assessed the impact. These figures document the impact of mostly mild atopic dermatitis on quality of life and highlight the difference in disease perception between parents and children.

It was also shown that atopic dermatitis severity scores were positively correlated with the CDLQI and DFI scores. These showed that any deterioration in eczema would lead to a decline in both family and children's QOL. The finding demonstrated the construct validity of the two instruments used to assess the QOL, despite the fact that both questionnaires were constructed and tested on patients from out patients departments. It also implies that the DFI and CDLQI can be used in a community-based study where most of the cases are mild. The impact on the family highlights the importance of considering the parents' input in the management of AD as the disease affects the entire family.

This study has also shown that DFI and CDLQI can change predictably with changes in disease severity, despite the fact that changes in disease severity were not statistically significant. This suggests that these questionnaires were able to change and could be used as an extra measure of outcome in every day clinical practice as well as in research studies.

4.4.4 Concluding remarks

- This is the first time that atopic dermatitis severity in the community has been studied prospectively and systematically using a valid and reliable scoring system by the same observer. It is also the first time that the impact of childhood atopic dermatitis documented in a structured way with the implementation of a longitudinal design in a community-based study. And also this is the first time that severity scores measured systematically have been correlated to quality of life scores that was measured by a published instrument at a single point and over a period of time.
- The study design in this thesis has overcome two well-recognised difficulties in atopic dermatitis definitions and epidemiology. First, the UK diagnostic criteria for AD were used as a disease definition. Second, by implementing the longitudinal prospective study design, the disease severity was accessible to be assessed consistently by the same observer, which would have been impossible in a retrospective survey. The potential confounding variables were recorded by a piloted and structured questionnaire prior to starting the study. This cannot be done in a retrospective study.

- Another strength of this study was the systematic assessment of disease severity and quality of life.
- It must be realised that this was a selected group of children with AD, and these data may not be applicable to all patients with AD in the population. These results should be interpreted with the limitation of potential selection and observer biases.
- This thesis has contributed to the body of knowledge regarding the principles and processes applied in the field of atopic dermatitis severity and its impact on quality of life. It identifies significant factors that have an effect on disease severity and the significance of these factors in the perception of health status in this group of patients. This may improve health care and bring the attention of health agencies to the impact of this stressful disease on individuals, family and the community as whole.
- In conclusion, this study has provided findings that stress the need for further research to assess more factors that influence AD severity over a longer period of time.

4.4.5 Issues for the future

The summary of other relevant findings not related to the aims of this study and lessons learnt from carrying out this study will be summarised in this section.

- The low response rate especially from the urban area (35%) highlights the difficulty in achieving enough subjects. It must be emphasised here that atopic dermatitis is a very common disease and affects about 15% of the UK population. Thus one should be cautious when carrying out research that involves the participation of large number of patients. Always think of a low response rate and ways of improving it.
- In any follow up study good relationships between the investigator and patients is necessary to achieve a low drop out rate. This can be simply accomplished by offering the patients enough time and by listening to them carefully.
- General practitioners should be actively involved in any study that requires subjects from a primary care setting. This may improve the response and follow up rates. GPs must be chosen randomly to avoid any selection bias. It also strengthens working relationships between primary and secondary care.

- Despite the fact that the UK diagnostic criteria were validated in community based-studies, 14 (10%) cases had or had had atopic dermatitis but did not fulfil the criteria. This highlights a potential difficulty in identifying every single case of atopic dermatitis.
- Severity assessment of atopic dermatitis is not an easy task despite using a potentially valid and reliable instrument. The various clinical presentations of the disease, extensor or flexural, localised or widespread expression and morphology of the lesions such as erythema that varies on a daily basis, and at the other end of the spectrum lichenification that usually takes days before changing, could explain some of difficulties. This enhances the case for standard markers (genetic, serological, biochemical) that represent AD severity without clinical examination.

4.4.6 Suggestion of further work

- It would be interesting to examine the same cohort of patients participating in this study, in 5 or 10 years time. This would provide further information on the association between risk factors and disease severity, in the long term. It would also improve our understanding of the natural history of the disease. Re-examining this cohort of patients may explore the relationship between eczema severity and development of asthma and/or hay fever later as well as the clearance rate, and the impact on quality of life in a longer term.

- Using the same design implemented in this study to carry out a more national study to document atopic dermatitis severity distribution in a representative sample from the whole UK. This can be achieved by inviting a random sample of GPs in the UK. From those GPs willing to participate, a random sample of patients with eczema should be taken. It should be emphasised that the ages should be clustered into 0-4, 5-8, 9-12, 13-16, 16-20, 21-30, 31-50 and more than 50. A representative sample of each age group would produce more detailed information about the impact of disease on each age group and the longitudinal design would explore the impact when the patients move from one age group into another. It could also explore and compare the association of risk factors with diseases severity from a longer-term study.
- Given the difficulties in assessing atopic dermatitis severity, there is a need to develop a genetic, immunological or biochemical marker for disease severity. Such studies should be very strict in case definition and patients with the same morphological features must be chosen. Also other factors such as asthma, or early onset that may underestimate or overestimate the validity of such a marker should be included in the analysis.

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6 Appendix

6.1 One-page questionnaire for historical features of the UK diagnostic criteria

Patient’s Name: Date:

Date of Birth: Telephone Number:

Could you please answer the following questions about your child’s skin?

(The answers simply require a tick (✓) in the appropriate box)

1. ‘Has your child had an itchy skin condition **in the last 12 months** ---
by itchy we mean scratching or rubbing the skin a lot? Yes ☐ No ☐
2. ‘How old was your child when this skin condition began?’

Under 2 years ☐

3 -4 years ☐

5 -10 years ☐
3. ‘Has this skin condition ever affected the skin creases in the past---
by skin creases we mean fronts of elbows, behind the knees,
fronts of ankles, around the neck, or around eyes?’ Yes ☐ No ☐
4. (a) ‘Has your child ever suffered from asthma-- by asthma
we mean bouts of wheezing or whistling in the chest?’ Yes ☐ No ☐
- (b) ‘Has your child ever suffered from hay fever--
by hay fever we mean bouts of sneezing, with
a runny nose and/or itchy eyes in the summer?’ Yes ☐ No ☐
5. ‘**In the last 12 months**, has your child
suffered from a generally dry skin?’ Yes ☐ No ☐
6. Has your child ever had eczema, by which, we mean
a scaly itchy rash mainly affects the skin creases? Yes ☐ No ☐ Don’t know ☐

6.2 Recruitment questionnaire

This questionnaire is completely confidential

St John’s Institute of Dermatology

Questionnaire about Atopic Dermatitis (Childhood Eczema)

Date:

/

/

Patient’s Name:.....

Sex:

M

F

(Please circle as appropriate)

Date of Birth:

/

/

Age:Years

Body weight:

.

Kilograms

OR

StonesPounds

Height:

.

Metres

OR

feet

Inches

Address:.....

.....

City:

Post code:Telephone:

ID Number: QAD(To be filled in by the doctor)

NHS Number:

How to complete this questionnaire?
Most questions simply require a tick (✓) in the appropriate box.

Appendix 6.2 continue

BACKGROUND INFORMATION ABOUT THE CHILD:

1. Birth weight: in Kilograms [] . [] [] or in Pounds [] [] . [] []

2. During which week in pregnancy did you give birth? [] [] Weeks

3. How many sister(s) and brother(s) does your child have? None []
1 []
2 []
3 []
4 []
5 or more, []

4. Country of birth:.....
If not the UK, for how long has your child has been living in the UK?
Less than 1 year []
1-2 years []
3-4 years []
5 years or more []

5. Which of the following categories do you feel best describes the ethnic group of your child?
White []
Black African []
Black Caribbean []
Black other []
Indian []
Pakistani []
Bangladeshi []
Chinese []
Other []
N/A []

6. BACKGROUND INFORMATION ABOUT CHILD’S MOTHER:

Name:
Address (if different from above):.....
.....
.....
Date of Birth: [] [] / [] [] / [] [] OR Age: [] [] Years
Country of Birth:.....
Are you employed at present? Yes [] No []
If yes, please specify

7. BACKGROUND INFORMATION ABOUT CHILD’S FATHER:

Name:
Address (if different from above):.....
.....
.....
Date of Birth: [] [] / [] [] / [] [] OR Age: [] [] Years
Country of Birth:.....
Are you employed at present? Yes [] No []
If yes, please specify

Appendix 6.2 continue

BACKGROUND INFORMATION ABOUT THE CHILD'S HOUSE/ FLAT:

8. Where is the house/flat where the child lives?
- | | |
|------------|--------------------------|
| Inner-city | <input type="checkbox"/> |
| Outer-city | <input type="checkbox"/> |
| Town | <input type="checkbox"/> |
| Village | <input type="checkbox"/> |
9. How far is your house/flat from a main road (busy road)?
- | | |
|--|--------------------------|
| On a main road | <input type="checkbox"/> |
| Approximately 100 metres (yards) or less | <input type="checkbox"/> |
| Approximately more than 100 metres (yards) | <input type="checkbox"/> |
| Don't know | <input type="checkbox"/> |
10. Do you keep any pets at home (house or garden)? No Pets ☐
- (Tick all that apply)
- | | |
|-----------------------------|--------------------------|
| Dogs | <input type="checkbox"/> |
| Cats | <input type="checkbox"/> |
| Birds (e.g. Canary, Parrot) | <input type="checkbox"/> |
| Other | <input type="checkbox"/> |
11. Do you have trees outside the house or on the road in front of the house?
- | | |
|-----|--------------------------|
| Yes | <input type="checkbox"/> |
| No | <input type="checkbox"/> |
12. Do you have fitted carpets in your home?
- | | |
|-----|--------------------------|
| Yes | <input type="checkbox"/> |
| No | <input type="checkbox"/> |
13. What is the type of heating used in your home? (Tick all that apply)
- | | |
|--------------------|--------------------------|
| No heating | <input type="checkbox"/> |
| Central heating | <input type="checkbox"/> |
| Electrical fire | <input type="checkbox"/> |
| Gas fire | <input type="checkbox"/> |
| Wood burning stove | <input type="checkbox"/> |
| Open fire | <input type="checkbox"/> |
14. How often do you vacuum clean/ Hoover the house/flat?
- | | |
|------------------------|--------------------------|
| Every day | <input type="checkbox"/> |
| Once or twice per week | <input type="checkbox"/> |
| Once a month | <input type="checkbox"/> |
| Less often | <input type="checkbox"/> |
| Never | <input type="checkbox"/> |
15. How many times was the child's mattress vacuumed during the last 12 months?
- | | |
|---------------|--------------------------|
| Once a week | <input type="checkbox"/> |
| Twice a month | <input type="checkbox"/> |
| Less often | <input type="checkbox"/> |
| Never | <input type="checkbox"/> |

INFORMATION RELATED TO THE WEATHER:

16. Which is the best season in the year for your child's eczema?
- | | |
|---------------|--------------------------|
| Winter | <input type="checkbox"/> |
| Spring | <input type="checkbox"/> |
| Summer | <input type="checkbox"/> |
| Autumn | <input type="checkbox"/> |
| No difference | <input type="checkbox"/> |

Appendix 6.2 continue

DETAILED INFORMATION ABOUT YOUR CHILD:

17. Was this child breast fed? No ☐
3 months or less ☐
More than 3 months ☐

18. At what age did she/he develop eczema? Less than 6 months ☐
7 to 12 months ☐
13 to 24 months ☐
3 to 6 years ☐
7 years or more ☐

19. Do any of the following suffer from or has she/he ever suffered from eczema, asthma, or hay fever? (Tick all that apply)

The child		Asthma <input type="checkbox"/>	Hay fever <input type="checkbox"/>	N/A <input type="checkbox"/>
Brother(s)/sister(s)	Eczema <input type="checkbox"/>	Asthma <input type="checkbox"/>	Hay fever <input type="checkbox"/>	N/A <input type="checkbox"/>
Father	Eczema <input type="checkbox"/>	Asthma <input type="checkbox"/>	Hay fever <input type="checkbox"/>	N/A <input type="checkbox"/>
Mother	Eczema <input type="checkbox"/>	Asthma <input type="checkbox"/>	Hay fever <input type="checkbox"/>	N/A <input type="checkbox"/>
Any of mother’s family	Eczema <input type="checkbox"/>	Asthma <input type="checkbox"/>	Hay fever <input type="checkbox"/>	N/A <input type="checkbox"/>
Any of father’s family	Eczema <input type="checkbox"/>	Asthma <input type="checkbox"/>	Hay fever <input type="checkbox"/>	N/A <input type="checkbox"/>

20. When your child first had eczema, how do you grade or rate his/her eczema on a scale of 0 to 10? Please circle as appropriate between 0 (no eczema) and 10 (the worst eczema your child has ever had).

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

21. If your child’s eczema flares up or gets worse does this affect her/his school achievement?

No change ☐
She/he does not like to go to school ☐
She/he cannot concentrate ☐
She/he can not play games or sport ☐
She/he is quiet in class ☐
Other reactions, please specify

22. Does your child’s eczema flare up or get worse while she/he is under stress such as around exam time?

Yes ☐ No ☐ Don’t Know ☐

23. Does your child’s eczema get worse while she/he is feeling hot (playing, sweating)?

Yes ☐ No ☐ Don’t Know ☐

24. Does your child’s eczema improve in the school holidays?

Yes ☐ No ☐ Don’t Know ☐

Appendix 6.2 continue

DETAILED INFORMATION ABOUT YOUR CHILD Cont....

25. At which age(s) has your child been free of eczema? (Tick all that apply)

Under 1 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐
Never free of eczema ☐

26. During the last year, how many days has your child missed/stayed away from school because of her/his eczema?

None ☐
1-3 days ☐
4-7 days ☐
2-3 weeks ☐
4 weeks or more ☐

27. How frequently has your child’s eczema got worse during the last 12 months?

None ☐
Every week ☐
Every fortnight ☐
Every month ☐
Every 2-3 months ☐
1 to 2 times per year ☐

28. In the past 12 months , how many times have you had to take your child to the doctor because of his/her eczema?

None ☐
Once ☐
2-3 times ☐
4-5 times ☐
6 times or more ☐

29. At the moment, how would you grade or rate your child’s eczema on a scale of 0 to 10? Please circle as appropriate between 0 (no eczema) and 10 (the worst eczema your child has ever had).

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

30. During the last 12 months, how many times has your child had a sore throat?

None ☐
Once ☐
Twice ☐
Three times ☐
Four or more times ☐

31. In the last 12 months, has your child been able to sleep well or has the eczema disturbed her/his sleep?

Sleep well ☐
Wakes up occasionally at night ☐
Often awake at night ☐
Seldom has a peaceful night ☐

INFORMATION ABOUT FOOD:

32. Are you aware of any kind of food which makes your child’s eczema worse?

Yes ☐ No ☐ Don’t know ☐

If yes, please specify

.....
.....
.....
.....
.....
.....
.....
.....

6.3 Follow-up questionnaire

This questionnaire is completely confidential

St. John’s Institute of Dermatology

FOLLOW-UP QUESTIONNAIRE
ABOUT ATOPIC DERMATITIS (CHILDHOOD ECZEMA)

Date: / /

Patient’s Name:

Age: Years

Address (only if you have moved house):
.....
.....

City:

Post code:

Telephone:

ID Number: QAD (To be filled in by the doctor)

NHS number:

How to complete this questionnaire?
Most questions simply require a tick (✓) in the appropriate box.

Appendix 6.3 continue

1. BACKGROUND INFORMATION ABOUT CHILD'S MOTHER:

Address (if different from above)
.....
.....

Are you employed at present? Yes ☐ No ☐
If yes, please specify
.....

2. BACKGROUND INFORMATION ABOUT CHILD'S FATHER:

Address (if different from above)
.....
.....

Are you employed at present? Yes ☐ No ☐
If yes, please specify
.....

BACKGROUND INFORMATION ABOUT THE CHILD'S HOUSE/ FLAT:

3. In the last 6 months, have you moved house? Yes ☐ No ☐
If no, please go to question number 8

4. Where is the **new** house/flat where the child lives? Inner-city ☐
Outer-city ☐
Town ☐
Village ☐

5. How far is your **new** house/flat from
a main road (busy road)? On a main road ☐
Approximately 100 metres (yards) or less ☐
Approximately more than 100 metres (yards) ☐
Don't know ☐

6. Do you have trees outside the **new** house
or on the road in front of the **new** house? Yes ☐ No ☐

7. Do you have fitted carpets in the **new** home? Yes ☐ No ☐

8. In the last 6 months, have you kept any pets
at home (house or garden)? (Tick all that apply) No Pets ☐
Dogs ☐
Cats ☐
Birds (e.g. Canary, parrot) ☐
Other ☐

9. In the last 6 months, what was the type of
heating used in your home? (Tick all that apply) No heating ☐
Central heating ☐
Electrical fire ☐
Gas fire ☐
Wood burning stove ☐
Open fire ☐

Appendix 6.3 continue

BACKGROUND INFORMATION ABOUT THE CHILD’S HOUSE/ FLAT
cont.:

10. In the last 6 months, how often did you vacuum clean/ Hoover the house/flat?
- | | |
|------------------------|--------------------------|
| Every day | <input type="checkbox"/> |
| Once or twice per week | <input type="checkbox"/> |
| Once a month | <input type="checkbox"/> |
| Less often | <input type="checkbox"/> |
| Never | <input type="checkbox"/> |
11. How many times was the child’s mattress vacuumed during the last 6 months?
- | | |
|---------------|--------------------------|
| Once a week | <input type="checkbox"/> |
| Twice a month | <input type="checkbox"/> |
| Less often | <input type="checkbox"/> |
| Never | <input type="checkbox"/> |

DETAILED INFORMATION ABOUT YOUR CHILD:

12. In the last 6 months, has your child suffered from attacks of
- | | |
|----------------------------------|--------------------------|
| None | <input type="checkbox"/> |
| asthma only? | <input type="checkbox"/> |
| hay fever only? | <input type="checkbox"/> |
| both asthma and hay fever? | <input type="checkbox"/> |
13. In the last 6 months, for how long has your child been free of eczema?
- | | |
|--------------|--------------------------|
| Not at all | <input type="checkbox"/> |
| One week | <input type="checkbox"/> |
| 2-4 weeks | <input type="checkbox"/> |
| 2-3 months | <input type="checkbox"/> |
| All the time | <input type="checkbox"/> |
14. How frequently has your child’s eczema got worse during the last 6 months?
- | | |
|------------------|--------------------------|
| None | <input type="checkbox"/> |
| Every week | <input type="checkbox"/> |
| Every fortnight | <input type="checkbox"/> |
| Every month | <input type="checkbox"/> |
| Every 2-3 months | <input type="checkbox"/> |
15. In the past 6 months , how many times have you had to take your child to the doctor because of his/her eczema?
- | | |
|-----------------|--------------------------|
| None | <input type="checkbox"/> |
| Once | <input type="checkbox"/> |
| 2-3 times | <input type="checkbox"/> |
| 4-5 times | <input type="checkbox"/> |
| 6 times or more | <input type="checkbox"/> |
16. During the last 6 months, how many days has your child missed/stayed away from school because of her/his eczema?
- | | |
|-----------------|--------------------------|
| None | <input type="checkbox"/> |
| 1-3 days | <input type="checkbox"/> |
| 4-7 days | <input type="checkbox"/> |
| 2-3 weeks | <input type="checkbox"/> |
| 4 weeks or more | <input type="checkbox"/> |

Appendix 6.3 continue

DETAILED INFORMATION ABOUT YOUR CHILD cont....

17. **At the moment**, how would you grade or rate your child's eczema on a scale of 0 to 10? **Please circle as appropriate** between 0 (no eczema) and 10 (the worst eczema your child has ever had).

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

18. **In the last 6 months**, has your child been able to sleep well or has the eczema disturbed her his sleep?

Sleep well
Wakes up occasionally at night
Often awake at night
Seldom has a peaceful night

19. **During the last 6 months**, how many times has your child had a sore throat?

None
Once
Twice
Three times
Four or more times

INFORMATION ABOUT TOPICAL STEROIDS:

20. **In the last 6 months**, how frequently have you applied steroid cream/ointment to your child's skin?

None
Less frequently
Every other day ☐
Once a day ☐
Twice a day ☐

INFORMATION ABOUT SYSTEMIC DRUGS:

21. Has your child received any of the following medicines (drugs) **in the last 6 months**?

None ☐
Antihistamines
Cyclosporin
Antibiotics
Azathioprine
Prednisolone

INFORMATION ABOUT HOSPITAL ADMISSION:

22. **In the last 6 months**, has your child been admitted to hospital because of her/his eczema?

Yes ☐ No ☐

If yes, for how long?

1 day
2-4 days
5-7 days
2-3 weeks
4 weeks or more

THANK YOU VERY MUCH FOR COMPLETING THIS QUESTIONNAIRE

6.4 Guidelines and definitions on how to use the SCORAD Index

Most of the following definitions and instructions copied from original article (European Task Force on Atopic Dermatitis, 1993).

A. Grading of Extent

The rule of nine is detailed in the front-back drawing on the evaluation sheet (Figure 3). Lesions taken into account must include only inflammatory lesions such as erythema, oozing/crusting and not dryness. In practice it is recommended to draw directly the extent of individual lesions on the printed figure of the evaluation sheet.

B. Intensity

1. Erythema. There is no problem to define this item on light-coloured skin. If grading is impossible, just mention it in the evaluation sheet (Figure 3) under remark.
2. Oedema/papulation. Oedema/papulation stands for palpable infiltration of the skin that may occur both in acute erythematous, excoriated lesions as well as in chronic lesions during flares. This item is difficult to define with clinical photographs. Thus palpation of the lesion should be taken into account in assessing this item.
3. Oozing/Crust. This item applies to exudative lesions resulting from epidermal edema and vesiculation.
4. Excoriation. This item is per se an objective marker for pruritus, more visible in nonlichenified lesions.
5. Lichenification. This item is synonymous with epidermal thickening in chronic lesions. Grossly accentuated skin furrows separate shiny rhomboid areas, and the colour is greyish or brownish.
6. Dryness. Whenever possible, this item should be appreciated at best at a distance from inflammatory lesions and without prior application of emollients/-moisturisers. Palpation is also important to assess the roughness of the skin (European Task Force on Atopic Dermatitis., 1993).

6.5 Hanifin and Rajka criteria for atopic dermatitis

Must have 3 or more basic features:

1. Pruritus. In which the diagnosis cannot be made in the absence of this criteria
2. Typical morphology and distribution:
 - Flexural lichenification or linearity in adults
 - Facial and extensor involvement in infants and children
3. Chronic or chronically-relapsing dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Plus 3 or more minor features:

1. Xerosis
2. Ichthyosis/palmer hyperlinearity/keratosis pilaris
3. Immediate (type I) skin test reactivity
4. Elevated serum IgE
5. Early age of onset
6. Tendency toward cutaneous infections (esp. *Staph.aureus* and *Herpes simplex*)¹
- impaired cell-mediated immunity
7. Tendency toward non-specific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor/facial erythema
16. Pityriasis Alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influenced by environmental/emotional factors
23. White dermographism/delayed blanch

The Hanifin and Rajka criteria mentioned above are copied word for word as cited in the original article (Hanifin and Rajka., 1980).

